MEDICAL BENEFIT OF PREEMPTIVE REPORTING OF PHARMACOGENOMIC INFORMATION FROM WHOLE EXOME SEQUENCING

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ABSTRACT

Douglas J Ball: Medical Benefit of Preemptive Reporting of Pharmacogenomic Information from Whole Exome Sequencing
(Under the direction of Jim Porto)

The effectiveness of utilizing individual patient's whole exome sequencing (WES) genetic information to influence patient care by predicting and preventing possible adverse drug reactions (ADRs) is investigated. Pharmacogenomically relevant variants from WES studies collected into two databases were analyzed to determine the expected medical benefit of reporting the incidental findings when WES studies are performed. One dataset was from UNC Chapel Hill as part of the NCGENES project database; the other was from Columbia University Medical Center's Whole Exome Research Database. The frequency of possible drug exposure for individuals in the US population was approximated by using data gathered from a database of outpatient drug prescribing, www.imshealth.org using the new prescription number data for 2014. Results were calculated to determine the aggregate number needed to screen (ANNS) to determine need for a change in medical management (different drug prescribing, monitoring, etc).

The NCGENES data utilized in this analysis included data from 672 individuals' genomes. The projected ANNS for this data set was 54.02. The calculated mean ANNS for the simulated data was 54.11, with a 95% confidence interval from 53.94 to 54.30 using Monte Carlo simulation (based on 1000 simulated points). CUMC data utilized in this analysis included data from 2,983 individuals' genomes. The projected ANNS for this data set was 46.15. Using Monte Carlo simulation, the calculated mean ANNS was 46.00 and the projected 95% confidence interval was from 45.93 to 46.08. Monte Carlo simulation of the error in these values was used to compute a 95% confidence interval, because of the complexity of estimating errors in these calculations.

Based on this analysis, the pharmacogenomically relevant impact of using WES based screening is in the range of 46 to 52 persons needed to screen when using incidental findings to dictate an expected

change in management. A model implementation plane for incorporating pharmacogenomic information into patient care within a healthcare system is provided and discussed

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CHAPTER 1: TOPIC AND INTRODUCTION

It is estimated that more than two million adverse drug reactions (ADRs) occur annually in the United States of America, resulting in over 100,000 deaths.[1] The number of ADRs is similar to the number of preventable medical errors that occur annually in the United States. However, unlike medical errors, ADRs are not currently considered to be preventable. Instead they are considered to be an unavoidable consequence of the practice of medicine. Evidence is mounting, however, that ADRs may not be unavoidable and are due partly to individual genetic variation.[2]

Herein the effectiveness of utilizing individual patient's genetic information to predict and prevent possible ADRs and treatment failures will be investigated. The field involving the study of the impact of individual genetic variation on drug therapy is generally known as either "pharmacogenetics" or "pharmacogenomics." This is an application of pharmacogenomics to patient care. This strategy is an alternative to the existing "one-drug-fits-all" approach to drug treatment. Although pharmacogenomics does not account for 100% of variability in drug response or adverse events, it is clear that certain specific genetic variants significantly affect outcomes of certain drug therapies.

The extremely rapid growth of knowledge in genetics has become a key feature of what has now been labeled as the "post genomic era." As a part of this, the clinical utility of this expanding knowledge of individual patient's genotypes has also been increasing rapidly. Whole Exome sequencing (WES) to aid in the diagnosis of genetic diseases has recently become available as a clinical tool for routine use in the United States. WES is a medical test in which all 20,000+ genes in the human genome are sequenced using what is now often termed next-generation sequencing.[3] WES is typically used to answer specific diagnostic questions, which are the focus of the report generated by laboratorians for the requesting clinicians.

One of the byproducts of such analysis is the sequencing of genes associated with the individual patient's potential response to drugs. WES is done for reasons other than pharmacogenomic evaluation,

and while pharmacogenomically important genes are sequenced, they are neither analyzed nor reported in most cases. The sole exception to this is a gene that is known to mediate malignant hyperthermia: RYR1 which is a member of a group of 56 high consequence genes that are typically reported as incidental finding that will be discussed in greater detail in Chapter 2[4]. Although the percentage of patients undergoing WES is currently relatively small, this number is expected to increase as sequencing costs continue to decline. Thus, the amount of genetic data generated from WES, and available for analysis and reporting, is expected to also rapidly expand.

Here, pharmacogenomically relevant variants from WES studies have been analyzed to determine the expected medical benefit of reporting the information when WES studies are performed. Two research databases of WES results were searched for pharmacogenomically significant variants, and population level data regarding drug utilization and drug-variant pair risk were used to create a model of clinical impact of variant reporting; one database was from UNC Chapel Hill and the other from Columbia University.

The researchable question is as follows:

What is the expected medical benefit of reporting incidental findings of pharmacogenomic significance from whole exome sequencing studies?

This analysis will require that the findings that meet standards of "pharmacogenomic significance" be determined. Significance will be decided by determining which pharmacogenetic variants are clinically actionable; these criteria are detailed in the methods section. Expected medical benefit will be reported as a predicted Number Needed to Screen (NNS), based on the frequency of clinically actionable pharmacogenomics variants in the WES patient population and the chance of drug exposure. Because genetically mediated risk in an individual depends both on the presence of a pharmacogenomically important variant, and the likelihood that the individual will be exposed to a drug for which that variant is important, a method of predicting the likelihood of relevant drug exposures will also be required. For this purpose, drug prescribing information, compiled from the general population of the United States, will be used.

Because of the complexity of implementing the use of such pharmacogenomics information in the healthcare system, a model implementation plan is provided and discussed. This implementation plan addresses the incorporation of this information into both the electronic health record (EHR) and the clinical decision support (CDS) system, based on current clinical informatics best practices.

To summarize, the key elements to be addressed are the following:

- Identifying and using timely sources of genetic information and pharmacogenomics knowledge;
- Modeling the clinical benefit of reporting incidental pharmacogenomics findings from WES;
- Presenting a model implementation plan for preemptive pharmacogenomics based on current clinical informatics best practices.

CHAPTER 2: LITERATURE REVIEW AND BACKGROUND

Genomic technology is developing at a breathtaking rate, and has the potential to change the way medicine is practiced in a variety of ways, bringing great opportunity while presenting multiple challenges. Several technologies have converged to provide the ability to compile large amounts of genetic and genomic information, which can then potentially be used in the care of the patient. The implementation of pharmacogenomics, however, is difficult because genetic testing and analysis is optimally done and results returned to the clinician before drugs are prescribed. This requires both that the provider is knowledgeable about pharmacogenomics, and that this patient-specific genomic information is available before the prescription is written. The clinical implementation of this "preemptive" testing strategy synthesizes knowledge from public health screening, next generation sequencing, and clinical informatics.

As with many health innovations, the utility of pharmacogenomics interests clinicians and scientists alike. Cohen reviewed and summarized the key values of pharmacogenomics to be 1) to decrease adverse drug reactions; 2) to optimize treatments based on a patient's unique genotype; 3) to enhance drug discovery; and 4) to improve efficacy trials.[5] Even though the cost of implementing any new technology is a concern, integrating pharmacogenomic information into pharmaceutical discovery pipelines should in theory reduce the cost of bringing drugs to market.[6]

In support of this proposed research and implementation plan, four broad areas of inquiry are particularly relevant. The first is the clinical benefit of pharmacogenomically informed prescribing, the second is access to pharmacogenomics knowledge, the third is the reporting of incidental findings produced by next generation sequencing assays, and the fourth is the implementation of pharmacogenomics into clinical practice.

By its very nature, pharmacogenomics involves the interactions and consequences of specific drugs with a specific gene (or sometimes a set of genes). The literature has many examples of specific

drug-gene pairs that are given to illustrate the broad concepts involved in pharmacogenomics, and how this discipline might change the delivery of care.

Common examples include Thiopurine and TPMT; Codeine and CYP2D6; and the interactions of Warfarin and the pair of genes VKORC1 and CYP2C9. The thiopurine methyltransferase (TPMT) gene has an impact on thiopurine therapy for acute lymphoblastic leukemia; TPMT pharmacogenomics can be used to identify patients at high risk of hematopoietic toxicity after thiopurine therapy.[7,8] Another often discussed gene is the hepatic cytochrome P450 gene CYP2D6, which is involved with the metabolism of many pharmaceutical agents. The impact of the CYP2D6 genotype or phenotype on the metabolism of codeine, a drug used for pain management, is often described. CYP2D6 polymorphisms affect both the effectiveness and safety of Codeine, and may dictate dose adjustments or choice of an alternate drug.[8,9]

Variation in drug effectiveness can also be influenced by genetic variation in drug receptors: a common example of this is variance in the molecular target of warfarin (the vitamin K-epoxide reductase protein), encoded by the gene VKORC1, which strongly influences the dose levels required by individual patients.[10] In 2005 it was demonstrated that, although neither VKORC1 nor CYP2C9 genotypes separately were effective predictors of interpatient variation in response to warfarin, the VKORC1 genotype together with the CYP2C9 genotype explained many differences in the response to treatment.[11] For all these drug-gene pairs, testing for the implicated genetic variant prior to drug prescribing might improve the safe and effective use of the drug (or use of a different drug if needed).

There is a growing body of literature looking at drug metabolism and response as a function of pharmacogenomic variants. Studies of pharmacogenomic response in twins have shown that in general between 20% and 95% of an individual's drug response is determined by genotype.[12] A systematic review in 2001 looked at drugs commonly implicated in adverse reactions, and concluded that knowledge of the genetic variants that lead to poor metabolism may guide prescribing that reduces adverse outcomes.[2] A systematic review in 2005 showed that there is good evidence of how genotypes influence drug prescribing, but "the "crucial data for assessing the value of Pharmacogenomics with regard to its impact on clinical practice and outcomes are currently lacking".[13] Since this time, pharmacogenomics knowledge has expanded, the number of reports in the literature has increased, and the focus has shifted

to improving outcomes and reducing harmful events. In 2014, Su et al reviewed the pharmacogenomic determinants of adverse drug reactions (ADRs) and summarized the state of progress.[14] They concluded that "thousands of genetic variations that are associated with drug safety and toxicity have been identified, many of which have shown high accuracy at predicting drug responses and adverse events."

However, despite the growing evidence for the role of pharmacogenomics in clinical care, use remains limited to specific instances of drug-gene pairs, and to a small number of centers nationally. In 2015, Dunnenberger HM, Crews KR, Hoffman JM, et al. documented the experience of five centers implementing preemptive pharmacogenomic testing, and concluded that over 98 percent of patients have at least one high-risk pharmacogenomic diplotype.[15] The work of these centers addresses the problems faced by pharmacogenomics; limited data on the utility of broad implementation of pharmacogenomics, and many barriers to implementation within patient care settings. More evidence of clinical utility and improved outcomes is needed to further the progress in this field.

Finding direct measures of utility in medicine can be challenging. One approach to the measurement of utility that has proved effective for public health screening is the number needed to treat (NNT), a concept published by Lapacus et al in 1988.[16] The NNT is the number of patients needed to treat to prevent one adverse case: it is the reciprocal of the absolute risk reduction due to a treatment or screening test. Absolute risk reduction is the difference in event rates between a control group and a screened or treated group. When used for a public health screening program, the reciprocal of the absolute risk reduction is often called the number needed to screen (NNS) rather than the number need to treat (NNT).[17]

Part of the application of a complex and rapidly changing body of knowledge is accessible and reliable sources of information that are adaptable and have been frequently updated to be relevant and safe. Thus, a key element to the adoption of pharmacogenomics into practice is the need to have continually updated knowledge databases in the field. Sources of information about pharmacogenomics that will be utilized in this dissertation include PharmGKB with its ranking of Very Important Pharmacogenes, the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for

prescribing based on gene variants, and the FDA guidance for Pharmacogenomic Biomarkers in Drug Labeling.

Initially developed as a research collaboration tool, PharmGKB is a centralized knowledge sharing site to facilitate data sharing which gives investigators with complementary data the ability to combine data sets. PharmGKB is facilitating the clinical implementation of pharmacogenomics, as curators also construct clinically relevant summaries of variant-drug associations.[18] Because of the quality of knowledge regarding these variants, they serve as a conservative set of variants for the exploration of the value of pharmacogenomics in our setting.

PharmGKB is a partner in the Clinical Pharmacogenetics Implementation Consortium.[19,20] CPIC guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy, rather than which tests should be ordered. [21] These Clinical Practice Guidelines will also be used to guide analysis of the clinical significance of variants.

The most heavily reviewed and curated drug information is available from the FDA. The FDA has developed a list of Pharmacogenomic Biomarkers in Drug Labeling. According to their website, FDA drug labeling information can include: “Drug exposure and clinical response variability, risk for adverse events, genotype-specific dosing, mechanisms of drug action, and polymorphic drug target and disposition genes.”[22] FDA labeling as it pertains to pharmacogenomic information may appear in several locations in the package insert, including Warnings and Precautions, Contraindications, Boxed Warnings, and Adverse Reactions.[23,24] Some, but not all, of the products have labeling that includes specific actions to be taken based on the biomarker information.

As pharmacogenomics information becomes more widely available, and the knowledge to direct its use becomes more accessible to a broader set of providers, how to obtain and to use this genetic information becomes important. One way of getting pharmacogenomics information is to order specific genetic tests or gene panels to determine a patient’s genotype and phenotype before prescribing certain drugs. As an example, preemptive TPMT genotyping prior to thiopurine treatment initiation in children with acute lymphoblastic leukemia has been recommended, and has been shown to be cost effective.[25] Another example is checking VKORC1 genotype together with CYP2C9 genotype before prescribing

Coumadin. Even though prior testing may decrease length of stay and cost over traditional dosing regimens, the cost of testing and delay in getting results limits the benefits.

Another way to get pharmacogenomics information in advance of prescribing decisions is to enhance access to genetic information from the expansion of genome and whole exome sequencing. The American College of Medical Genetics and Genomics has noted that with clinical exome and genome sequencing, there is a potential for the "recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing, but of medical value for patient care." The term "incidental findings" or "secondary findings" refers to genetic variants that are those other than what the test was ordered for, which are termed "diagnostic findings" or "primary findings." Incidental findings can be further subdivided into "Unintended" (e.g. Huntington's disease), "Screening" (which include pharmacogenomic findings and risk alleles), and "Uninformative" (includes Variants of Unknown Significance).

In May 2012, the American College of Medical Genetics and Genomics issued a recommendations statement suggesting incidental reporting of 56 genes, with pre-test consent of the patient.[4] These recommendations have been criticized because of the uncertainty about the penetrance and scope of expressivity for many of the genes. In addition, critics have pointed out a lack of clarity in clinical utility, as well as ethical questions about not providing the option to decline incidental reporting when undergoing testing.[26,27] Although the debate about the clinical utility and ethics of reporting incidental findings is ongoing, with only a single exception, the 56 genes recommended by the American College of Medical Genetics and Genomics are not considered to be pharmacogenes. Only one of these is specifically on the list as a pharmacogene due to its impact on drug prescribing, although several others may have implications for drug use in addition to other clinical recommendations. An example is long QT syndrome, where in addition to recommendations to avoid drugs which prolong the QT interval, other medical and behavioral recommendations are associated with the genetic variant.

Recommendations for reporting of incidental findings are predicated on an understanding of what to do with the results. Berg et al looked at incidental findings, and categorized the results as follows: Clinically Actionable, Clinical Valid but not Actionable, and Uninformative. Pharmacogenomic variants in

this scheme were categorized as being clinically valid but not actionable, because the risk to patients only occurs with treatment by a specific drug, which may never be prescribed.[28] However, for some pharmacogenomics variants, or very commonly prescribed drugs, the utility of reporting these findings should be linked to the act of prescribing these drugs. This is because the risk of adverse events in persons with these specific Pharmacogenomics variants is high, in some cases life- threatening. As an example, children who are ultrarapid metabolizers of codeine can be given a life-threatening dose if their status is not known, because they immediately metabolize codeine to morphine resulting in toxic levels of this opioid. Thus, for those patients exposed to that specific drug, this "incidental finding" goes from clinically irrelevant, to critical to avoid over-dosing of the drug. The concept of providing pharmacogenomics information as a precursor to drug prescribing in certain susceptible individuals sets the stage for a discussion of how to incorporate available pharmacogenomic information into the medical record in a way that will inform safe drug prescribing.

There is growing evidence for the clinical benefit of preemptive genomic testing prior to pharmaceutical prescribing, to guide decision making. Preemptive testing is particularly useful when implemented with informatics tools such as clinical decision support within a broader program. Using the combination of incidental findings from WES with preemptive pharmaceutical prescribing has not been described in the literature, with the exception of the single pharmacogene recommended by the ACMG for incidental reporting. Delineating the clinical benefit of pharmacogenomics, particularly preemptive pharmacogenomics, in combination with the issues around the reporting of pharmacogenomics variants, and an understanding of the need for point-of-care information and decision support, are all important aspects of the implementation of pharmacogenomics into the healthcare system. A more detailed discussion of the literature as it applies to such implementation can be found in Chapter 5: Model Implementation Plan.

CHAPTER 3: METHODS

Pharmacogenomic knowledge is evolving at a rapid pace. For the purpose of this work, the guidelines and recommendations current as of July 1, 2016 were used. While it is certain that these guidelines will evolve over time, it is necessary for a thoughtful analysis. The reader should keep this in mind.

DATA SOURCES

Two different whole exome sequence databases were analyzed; both of these databases were developed with other research in mind and were made available for this work. The first was from UNC Chapel Hill as part of the NCGENES project database; the other was from Columbia University Medical Center's Whole Exome Research Database. UNC Chapel Hill IRB exemption was provided to this project for both data sets after application for review. In addition to these two data sets, information about allele frequencies was obtained from PharmGKB (www.pharmgkb.org). This is a website with curated genomic information and summaries of allele and genotype frequencies based on compiled literature. This allele and genotype frequency information was used to represent the general population. In addition, curated allele frequency data from the 1000 Genomes project was used to generate control values for comparison, when PharmGKB data were lacking. This database was selected because of usability. Importantly, the NCGENES project data, and Columbia University Whole Exome data differ from those taken from PharmGKB and the 1000 Genomes project. The latter curated data sets represent the best available data, using all methodologies (especially PharmGKB) and with techniques optimized for analyzing pharmacogenes and their complex allele variants. Some of these variants have not been captured in the convenience samples from NCGENES and Columbia University Medical Center, which used more general sequencing protocols that were not optimized for this purpose. These two samples

and the population data were used for comparison calculations, to help to determine the gap between incidental findings from WES, and the expected results based on current scientific knowledge.

	NCGENES	CUMC	PharmGKB
# of participants	672	2,983	Variable; aggregate data from many sources
Population	Adult and pediatric patients at University of North Carolina hospitals	Adult and pediatric patients at Columbia University Medical Center Hospitals	International; variable, aggregated from peer-reviewed literature on PGx
Type of test	Whole exome sequencing	Whole exome sequencing	Multiple; real-time Polymerase Chain Reaction (PCR), microarray technology (gene chip)
Intent of test	Diagnostic and research exomes. Not obtained for PGx purposes.	Diagnostic and research exomes. Not obtained for PGx purposes.	Pharmacogenomic testing

TABLE 1: COMPARISON OF DATA SOURCES.

A list of clinically actionable variants was compiled, based on drug-gene pairs that have CPIC A status or Clinical Guidelines. Also included were any drugs with FDA labeling of Actionable, Genetic Testing Required, or Genetic Testing Recommended from the FDA Table of Pharmacogenetic Markers in Drug Labeling. The list of drugs with FDA labeling pertaining to pharmacogenomics, and the labeling excerpts and CPIC levels are listed in Appendix A. Appendix B has the drug and CPIC guideline information.

A useful concept in pharmacogenomics is that of “drug-gene pairs”; these are the combination of a specific gene and a specific drug that is a reason for concern due to potential risk, or possible need for modification of clinical care. However, simply knowing the gene in which a variant occurs is often not enough for this analysis. There often are several distinct variants within a given gene that have different implications for the same drug, and whether an individual has one or two of variants is also sometimes important. So in this analysis the term drug-genotype pair will be used to reflect this complexity. Appendix C has drug-gene pairs, based on the list of drugs in Table 1. Appendix D is the table of allelic variant combinations that was used to predict phenotype/gene function.

To determine the likelihood that a hypothetical individual might have a gene variant that would be important in his or her healthcare, both the chance that the individual has the gene variant and that chance that the individual is exposed to an impacted drug must be determined (in the general population) for each variant. This frequency of drug exposure for individuals in the US population was approximated by using data gathered from a database of outpatient drug prescribing, www.imshealth.org. This has been provided for the drugs of interest for the United States. This data includes TRX, the total prescription number data, and NRX, the new prescription number data for 2014. NRX is used for the projected new exposures to medications, though it should be noted that for certain drugs with chronic use it may overestimate the true naive exposures rate because while refills are not captured as part of NRX, all new prescriptions are, even if the patient is already on that medication. In addition to population level data on frequency of drug exposure, population level data on allele frequencies was also used as a comparison and for further analysis.

The list of drugs that was requested from IMS health is below in table 2.

abacavir	Fluorouracil	Sertraline
allopurinol	Fluvoxamine	Simvastatin
amitriptyline	Imipramine	Succinylcholine
aripiprazole	Irinotecan	Sulfasalazine
atomoxetine	Ivacaftor	Tacrolimus
azathioprine	mercaptopurine	Tamoxifen
boceprevir	methylene blue	propafenone
capecitabine	nitrofurantoin	protriptyline
carbamazepine	norfloxacin	rasburicase
celecoxib	nortriptyline	Ribavirin
chloroquine	oxycodone	Telaprevir
citalopram	paroxetine	tetrabenazine
clomipramine	peginterferon alfa-2a	thioguanine
clopidogrel	peginterferon alfa-2b	thioridazine
clozapine	phenytoin	Tramadol
codeine	primaquine	Trimipramine
dapsone	probenecid	Voriconazole
desipramine	propafenone	Warfarin
doxepin	protriptyline	
escitalopram	rasburicase	
esomeprazole	Ribavirin	

TABLE 2: LIST OF DRUGS FOR WHICH DATA WAS REQUESTED FROM THE IMS HEALTH FOUNDATION

For each drug, there are known allelic variants in pairs for genotypes of pharmacogenomic significance. Genotypes for each combination of alleles were calculated; then the genotypes (and corresponding phenotypes) were evaluated for recommended clinical actions. These actions vary based on the genotype and corresponding phenotype, and may include:

1. Dose adjustment
2. Monitoring of clinical response (i.e. depression or pain)
3. Monitoring of serum drug levels (i.e. imipramine)
4. Monitoring of labs (i.e. Creatine Kinase or Liver Function Tests)
5. Drug discontinuation or use of an alternative agent
6. Targeted drug use (i.e. ivacaftor)

The following information was reported for the data sets from NCGENES and Columbia University Medical Center:

1. The number of Whole Exome Sequences used in the analysis.
2. Frequency of patients with clinically actionable genotypes, based on drug-gene pairs.
3. Likelihood of indicated clinical action with each specific drug based on phenotype.

Allele frequencies were obtained for ancestry groups that most closely represent Whites, Blacks, and Asians in the United States. These ancestries were classified slightly differently depending on the database (and original research population). The 1000 genome project has population data for African Ancestry in the Southwest US, East Asian ancestry, and Utah residents with Northern and Western European ancestry. PharmGKB refers to these same ancestry groups as Caucasian (excluding European), African American, and East Asian. Note that these groups are considered useful surrogates for the larger population of Whites, Blacks, and Asians in the United States. U.S. Censes population data were used to race adjust these allele frequencies based on ethnic groups for the general US population (www.census.gov). The U.S. Census year of 2015 was used; at that time the US total population was 321,418,820. Proportionally, Whites were 77.01% of the population, Blacks or African Americans were 13.26%, and Asians were 5.6%. The other races that were not used in this calculation due to lack of genetic data were American Indian, Alaskan Native, Native Hawaiian and other Pacific Islander, and

those with two or more races represented. Together these groups represent <5% of the population of the United States.

ANALYTICAL METHODS

This data were used to derive a mathematical model that generated the expected need for change in clinical care based on a projected Number Needed to Screen (NNS). The Number Needed to Screen was calculated for the NCGENES data set, the Columbia University data set, and for the general population of the U.S. based on published allele frequencies. This result is reported as a composite NNS for all drug-gene pairs for NCGENES and for the Columbia University Medical Center data. The predicted NNS for the entire United States population was also calculated as a population-based estimate using published allele frequencies.

For a population with genotype-related adverse event frequency **a** and non-genotype-related adverse event frequency **c**, the following two by two table applies.

Population exposed to a specific drug		
	Adverse Event	No Adverse Event
Pharmacogene Variant	a	b
No Pharmacogene Variant	c	d

TABLE 3: TWO BY TWO TABLE DEPICTING COMPONENTS OF POPULATIONS EXPOSED TO A SPECIFIC DRUG WITH A SPECIFIC PHARMCOGENE VARIANT

Absolute Risk Reduction (ARR) is given by:

$$ARR = \left(\frac{c}{c+d}\right) - \left(\frac{a}{a+b}\right)$$

The number needed to screen (NNS) is the reciprocal of this number:

$$NNS = \frac{1}{\left(\frac{c}{c+d}\right) - \left(\frac{a}{a+b}\right)}$$

Rather than calculating only the NNS for one drug-gene pair, a NNS applying to all drug-gene pairs at once is required. To accomplish this task, an aggregate number needed to screen (ANNS) is proposed. Like the NNS above, this is the reciprocal of the ARR, however, in this case it is the aggregate absolute risk reduction (AARR). The relative risk reduction is defined for individuals with a specific drug-genotype combination. This needs to be accounted for in the aggregate absolute risk reduction and aggregate number needed to screen. For the multiple drug-gene pairs, the aggregate absolute risk reduction is given by:

$$\text{AARR} = \sum_1^n d_i g_i ARR_i$$

Where d_i is the risk of having a drug exposure and g_i having the corresponding genotype. Then,

$$ANNS = \frac{1}{AARR}$$

$$ANNS = \frac{1}{\sum_1^n d_i g_i ARR_i}$$

And,

Confidence intervals for the projected ANNS were also calculated. A confidence interval for the ANNS could be obtained by taking reciprocals of the values defining the confidence interval for the aggregate absolute risk reduction.

The standard error for the absolute risk reduction for a single drug-genotype pair is given by,[29]

$$SE = \sqrt{\left(\left(\frac{R_1(1-R_1)}{n_1}\right) + \left(\frac{R_2(1-R_2)}{n_2}\right)\right)}$$

Using the general equation of orthogonal standard error,[29] Statistic ± 1.96 $SE_{statistic,}$ the 95% confidence interval for the absolute risk reduction is given by ARR_i+1.96SE_i to AARR-1.96SE_i

And by back substitution, the confidence interval for the ANNS is given by the reciprocal of this interval, if d_i, and gi are assumed to have only small errors, as follows:

$$\frac{1}{\sum_1^n d_i g_i (ARR_i + 1.96SE_i)}, \frac{1}{\sum_1^n d_i g_i (ARR_i - 1.96SE_i)}$$

However, it is hard to generalize about the precision in which d_i, and gi are known in our data sets, and the error in these coefficients may be significant. Also, because we are relying on multiple studies in the literature for these data (as collected and curated by PharmGKB), SE_i is not available for all drug-genotype pairs. For these reasons Monte Carlo simulation has been employed to analyze the sensitivity of the 95 percent confidence interval errors in these values.[30]

While it was an initial hope that an aggregate ARR for different adverse events could be computed, such detailed data were not available for all the terms in the calculation and that goal was abandoned based on the available literature. Instead only the question of whether a change in clinical management was indicated based on genotype was addressed. For this analysis the ARR is taken as 1, which makes the error contributed from the ARR term trivial. However, the error contributed from the genotype frequency, and the drug exposure risk are neither clearly available in the literature for each drug gene pair, nor in our data sets, nor analytically straightforward to determine.

When considering the chance of having a specific allele or pair of alleles, the binomial distribution describes the chances. This is also the case when considering if a drug exposure occurs or not. In both of these instances standard error can be described in terms of p (the chance of having or not having an

exposure or a drug), and N (the number of observations). For genotype, the N needs to be multiplied by 2 because of there are two alleles typically per observation.

The binomial standard error is then given by,

$$SE = \sqrt{\frac{p(1-p)}{N}}$$

Because for genotype observations there are 2N allele observations for N subjects the binomial standard error is given by,

$$SE = \sqrt{\frac{p(1-p)}{2N}}$$

Unfortunately, the number of observations, N, is not available for all curated data for the allele frequencies from PharmGKB, however, approximate values are available that can serve to bound the standard error from above.

Because of the complexity of the product of these errors for each term in the ANNS calculation, and the uncertainty in these values, Monte Carlo simulation of the error in these values was used to compute a 95% confidence interval for the ANNS. For those parameters which a standard deviation is known, it is utilized in the Monte Carlo simulation; for those in which it is not known, the methodology of determining the plausible range of each variable outlined by Peter Muennig is empolyed.[31]

When the parameter is based on an assumption or expert opinion it is tested over a very broad range of values. Expert opinion is also used to determine plausible high and low values when available. When the parameter is obtained from a random sample, the 95 percent confidence interval for the parameter is used.

The mathematical model and numerical simulation was conducted using a licensed copy of SAS9.4 . The program code is provided as Appendix E, F and G.

Results for CUMC and NCGENES data sets were confirmed by replicating the calculations using Excel which excluded the Monte Carlo simulations.

CHAPTER 4: RESULTS

The Pharmacogenomics data from FDA drug labels and CPIC A guidelines were reviewed. There were a total of 48 drugs that met our criteria; 38 had pharmacogenomic information on the FDA label, 46 had CPIC A levels, and 30 had both.

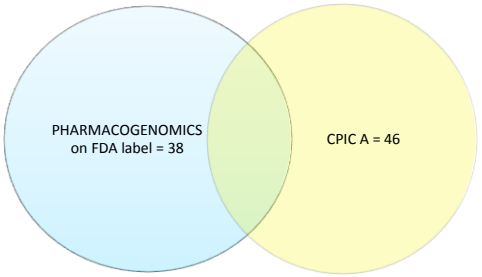

FIGURE 1: A VENN DIAGRAM DEPICTING OVERLAP BETWEEN CPIC CATEGORY A DRUGS AND DRUGS WITH PHARMACOGENOMICS INFORMATION ON FDA LABEL.

The results of the drug request from IMS Health are below: the table has the drug name and the number of new prescriptions for the year 2015 nationally.

Drug Name	New RX #
ABACAVIR	44080
ALLOPURINOL	6192623
AMITRIPTYLINE	6170974
ARIPIPRAZOLE	4747675
ATOMOXETINE	1313449
AZATHIOPRINE	676708
BOCEPREVIR	303
CAPECITABINE	86800
CARBAMAZEPINE	1842873
CELECOXIB	4003495
CHLOROQUINE	66824
CITALOPRAM	15433189
CLOMIPRAMINE	192397
CLOPIDOGREL	8620060
CLOZAPINE	749014
CODEINE	76869
DAPSONE	717082
DESIPRAMINE	118670
DOXEPIN	1301955
ESCITALOPRAM	12901839
ESOMEPRAZOLE	5723341
FLUOROURACIL	722640
FLUVOXAMINE	509629
IMIPRAMINE	444363
IRINOTECAN	724
IVACAFTOR	1037
MERCAPTOPURINE	189240
METHYLENE BLUE	59
NITROFURANTOIN	8100477

NORFLOXACIN	2550
NORTRIPTYLINE	1773482
OXYCODONE	23283753
PAROXETINE	6501057
PEGINTERFERON ALFA 2A	17553
PEGINTERFERON ALFA 2B	4560
PHENYTOIN	1737817
PRIMAQUINE	3414
PROBENECID	80691
PROPAFENONE	264793
PROTRIPTYLINE	19969
RASBURICASE	6
RIBAVIRIN	65958
SERTRALINE	19036779
SIMVASTATIN	24523203
SUCCINYLCHOLINE	169
SULFASALAZINE	541140
TACROLIMUS	808518
TAMOXIFEN	551094
TELAPREVIR	251
TETRABENAZINE	4043
THIOGUANINE	1878
THIORIDAZINE	76088
TRAMADOL	30859928
TRIMIPRAMINE	1805
VORICONAZOLE	37999
WARFARIN	16437806

TABLE 4: IMS HEALTH FOUNDATION DRUG DATA FOR THE UNITED STATES IN 2014

The drugs were sorted by frequency of prescribing; the following are the 10 most commonly prescribed drugs with pharmacogenomic significance in the United States in 2014.

Drug Name	# New Rx	Frequency
TRAMADOL	30859928	14.9
SIMVASTATIN	24523203	11.8
OXYCODONE	23283753	11.2
SERTRALINE	19036779	9.17
WARFARIN	16437806	7.92
CITALOPRAM	15433189	7.43
ESCITALOPRAM	12901839	6.22
CLOPIDOGREL	8620060	4.15
NITROFURANTOIN	8100477	3.9
PAROXETINE	6501057	3.13

TABLE 5: TEN MOST COMMON DRUGS FROM THE LIST REQUESTED FROM IMS HEALTH FOUNDATION FOR THE UNITED STATES IN 2014

The NCGENES data utilized in this analysis included data from 672 individuals' genomes. This data analysis resulted in the identification of 223 individual genotypes that were potentially clinically actionable with exposure to relevant drugs. 180 people would require dose reduction, 40 people would

require an alternate drug, and 3 people would require serum monitoring. The projected ANNS for this data set was 54.02. The calculated mean ANNS for the simulated data is 54.11, with a 95% confidence interval from 53.94 to 54.30 using Monte Carlo simulation (based on 1000 simulated points). See Appendix I for the complete listing of alleles, genotype, drug exposure, phenotype, action, and ARR.

The following were the proportions of different actions based on the genotype and phenotype, for the NCGENES data set (Table 6).

Possible Action	Frequency
Dose adjustment	**80.7%**
Drug discontinuation or use of an alternative agent (i.e. clopidogrel)	**17.9%**
Monitoring of serum drug levels (i.e. voriconazole)	**1.3%**

TABLE 6: PROPORTIONS OF DIFFERENT ACTIONS BASED ON THE GENOTYPE AND PHENOTYPE, FOR THE NCGENES DATA SET

CUMC data utilized in this analysis included data from 2,983 individuals' genomes. This data analysis resulted in the identification of 1,483 genotypes that were potentially clinically actionable with exposure to relevant drugs. The projected ANNS for this data set was 46.15. Using Monte Carlo simulation, the calculated mean ANNS is 46.00 and the projected 95% confidence interval is from 45.93 to 46.08. See Appendix J for the complete listing of alleles, genotype, drug exposure, phenotype, action, and ARR.

The following were the proportions of different actions based on the genotype and phenotype, for the CUMC data set (Table 7).

Possible Action	Frequency
Dose adjustment	**59.7%**
Drug discontinuation or use of an alternative agent (i.e. clopidogrel)	**27.9%**
Monitoring of serum drug levels (i.e. voriconazole)	**12.4%**

TABLE 7: PROPORTIONS OF DIFFERENT ACTIONS BASED ON THE GENOTYPE AND PHENOTYPE, FOR THE CUMC DATA SET.

Importantly, CYP2D6 could not be adequately evaluated based on the variants called by the NCGENES and CUMC data sets. This was due to both their complexity, and the unavailability of phase information, thus CYP2D6 variants were excluded from the analysis.

General population data were used as a comparison, using the same guidelines and new prescription (NRX) data; this calculation was completed using genotype frequency data from PharmGKB and 1000 Genome project for the United States. The calculated ANNS from the published data is 5.79 people. The mean ANNS is 5.732 people with a projected 95% confidence interval of 5.72 to 5.76 based on Monte Carlo Simulation of variation in the data.

CHAPTER 5: MODEL IMPLEMENTATION PLAN

While the use of pharmacogenomic data in clinical practice is growing, the information is generally used in a retrospective manner. The focus is on adverse drug events, and specific tests are generally done on individuals to help with clinical decision making.[32] In the future, if pharmacogenomics can be proven to be cost effective and clinically useful, much more pharmacogenomic testing should be done preemptively, with a goal of having the data on hand for prevention of toxicity and for treatment optimization at the moment that a prescribing decision is entertained. This would necessitate a change to either population-wide screening or screening of appropriately selected sub-populations as well as the use of large databases to store the information, and a mechanism for the provision of Pharmacogenomics results at point of care; thus shifting the focus to the selection of appropriate drug therapy based on knowledge of the patient's pharmacogenomic phenotype.

Several institutions that are part of the Translational Pharmacogenetic Program have published some of their early experiences with their efforts to implement such approaches into their respective healthcare systems; this model plan is heavily influenced by their experiences. These institutions include Mayo Clinic, Ohio State University, St. Jude Children's Research Hospital, University of Florida, University of Maryland, and Vanderbilt University Medical Center University of Chicago and Brigham and Women's Hospital.

While the current research has focused on the determination of the utility of reporting variants found in WES to guide patient management, ideally a model implementation plan would use these WES data more broadly. A model implementation plan to use these data would not need to be coupled directly with its source, and indeed could be expected to be the same for many sources of pharmacogenomics data, including WES as we have explored, as well as pharmacogenomic panels done specifically to aid drug prescribing.

Once a means of obtaining these data consistently is available, the next step in integrating it into routine patient care will be laying the groundwork for implementation of preemptive reporting in the Electronic Health Record (EHR). Such reports will need to include information about the abnormal genotype, and well as prescribing guidance. Because "alert fatigue" is now a well-recognized consequence of EHRs, active interruptive alerts should probably be only be reserved for high significance results. The knowledge needed to act on pharmacogenomic information is currently rapidly evolving, thus a way to provide information passively will also be desirable. Thus, both passive information and active alerts are recommended as part of Computer Decision Support (CDS) in this model implementation plan.

BARRIERS TO IMPLEMENTATION

While the knowledge base and literature support for the use of pharmacogenomics to effect patient care is expanding, there still remain many barriers that the utilization of pharmacogenomics information to change prescribing practice (see Table 8).[15,32,33]

Barriers to Implementation
Lack of availability of results
Lack of clinical education and guidance on how to use pharmacogenomics data in clinic
Lack of acceptance of need for pharmacogenomics-directed prescribing
Clinicians' resistance to using genetic data in clinical practice
Absence of infrastructure to handle genetic data
Cost and reimbursement issues
Time, workflow, and efficiency

TABLE 8: BARRIERS TO IMPLEMENTATION

First, pharmacogenomics information is not readily available in many settings. Clinicians without access to both pharmacogenomics information and pharmacogenomics results can be expected continue to prescribe medications as they always have, due either to lack of knowledge of the risks for adverse events, or due to an inability to easily obtain pharmacogenomics information. For example, codeine is still prescribed to patients whose CYP2D6 genotype is not known, despite strong evidence that patients who are CYP2D6 poor metabolizers are not likely to experience analgesia, and ultrarapid metabolizers are at increased risk of toxicity. Studies of both physicians and pharmacists show that education about the utility of pharmacogenomics is inadequate.[34-36] While the capability to conduct pre-prescribing genetic testing has been available for over ten years for some therapies, such testing has not become routine for

most practitioners. In a survey of nearly 400,000 US physicians by Stanek et al in 2012, only 10.3% felt adequately informed about pharmacogenomic testing, only 12.9% had ordered testing within the prior 6 months, and only 29.0% had received any education regarding pharmacogenomics. Despite relatively low response rates, the authors concluded that lack of effective physician education on the clinical value, availability, and interpretation of pharmacogenomic tests was a significant cause of poor uptake of pharmacogenomics in physician practices.[33] Clinician education needs to include information about what tests are available, how to procure them, and how to interpret and apply the results to the patient's care.[34,37]

The lack of generalized acceptance of the need for pharmacogenomic testing to be incorporated into clinical decision making is multifactorial. Issues include ingrained provider prescribing habits, and the timing of when computer decision support (CDS) alerts are provided. Hayward showed that delivering suggestions for drug change at the moment of prescribing may be "too late" for the provider to change his/her decision-making process; rather, this information needs to be presented before the provider has decided what drug to use and started entering the order.[38] Knowledge of how to use pharmacogenomic test results is also critical, and will require either improved provider education, or enhanced clinical decision support in the Electronic Health Record, or both. As the pharmacogenomics knowledge continues to grow, a means of concomitantly updating the CDS system and developing provider knowledge should be considered.

The current way providers treat patients most often takes place in the absence of patient-specific information about pharmacogenomics variants, with a lack of personal knowledge of how to use the results, and without education or CDS to help with prescribing decisions. This decision flow is diagramed below (see figure 2).

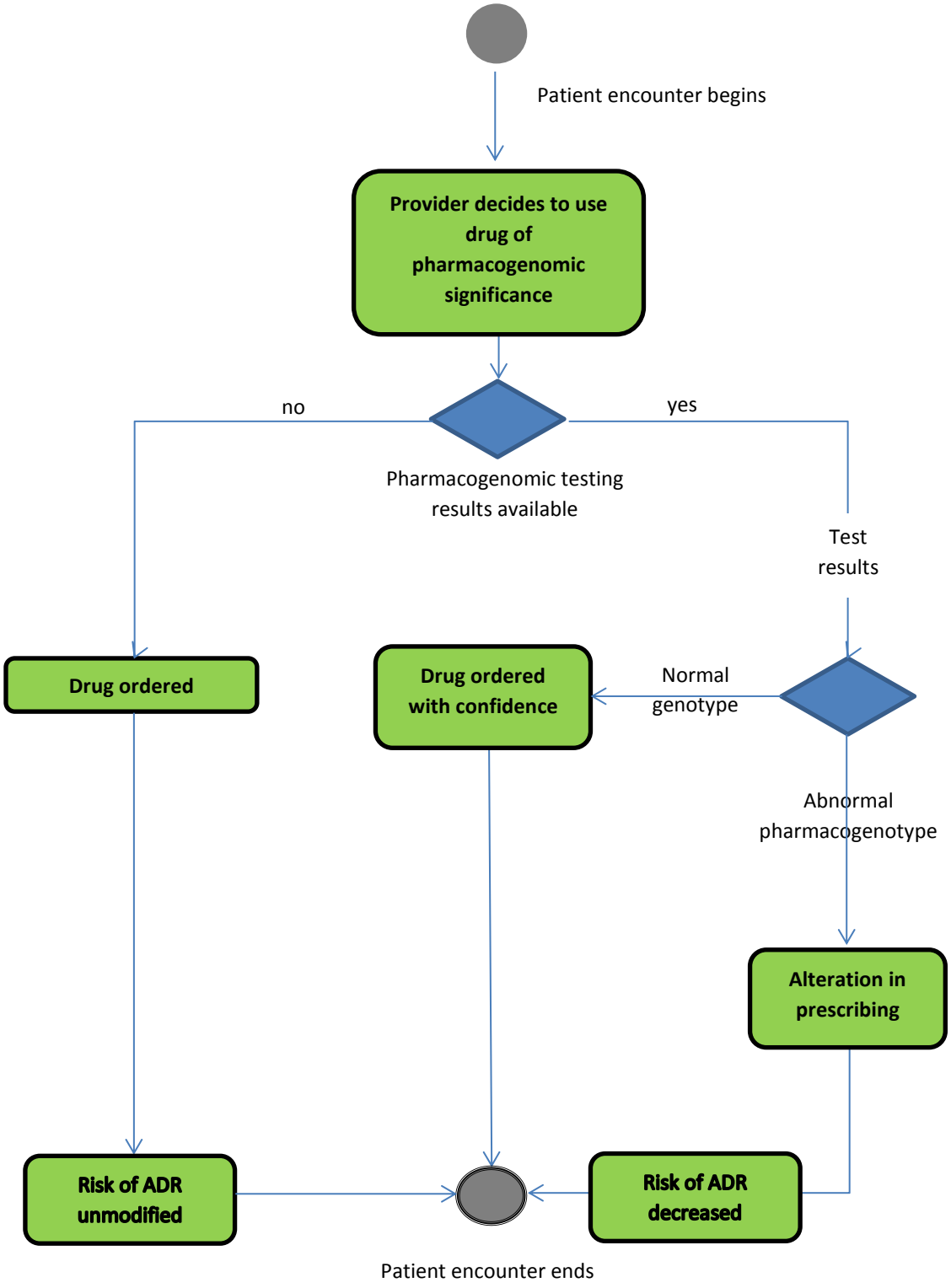

FIGURE 2: THE CURRENT REACTIVE APPROACH TO DRUG PRESCRIBING, WHICH DOES NOT TAKE INTO ACCOUNT THE PHARMACOGENOMICS VARIANT STATUS.

Cost is another barrier often cited to implementation of pharmacogenomics into care; reimbursement for genetic testing and interpretation hopefully will improve as the utility and cost savings in the prevention of adverse events becomes clearer, but so far there is little evidence that this is the case. Of course one of the benefits of using WES data is that it is already available. However, there is still a cost to reporting the additional results in terms of laboratorian time, the provision of passive interpretive information in the EHR, and the use of CDS with technical support for decision alerts. This represents an additional barrier to implementation.

ELEMENTS NEEDED FOR IMPLEMENTATION:

Results of Whole Exome Sequencing will need to be made available for clinician use; in our data sets, these WES results were incidental findings for a different clinical question. However, going forwards either WES results or Whole Genome Sequencing (WGS) results, or targeted and optimized pharmacogenomics panels can be used depending on the institution and the sub-population of interest. The clinical genotype will need to be reported, based on translating variants into genotypes, and their associated phenotypes. Based on the analysis of benefits of reporting genotypes, decisions will need to be made about which genotypes and associated phenotypes to report. Genotypic and phenotypic information, and its relevance to prescribing, will then need to be placed into the Electronic Health Record.

In their article, Marsolo and Spooner identify five core EHR functions that are needed if genomic information is to be used in clinical care.[39] These include:

1. Storing genetic information as structured data;
2. Standards based data to allow the information to move between different EHR systems;
3. Rich phenotypic information which is stored as structured data and associated with relevant genetic information;
4. Data made available for use by rules-based decision-support engines; and
5. An EHR which can obtain and display information needed by the clinician to interpret the genotypic and phenotypic data.

Ideally, this information will be furnished to the provider prior to the decision about which drug to order. In addition, if the provider enters a medication order, it would be desirable for the patient's phenotype to be furnished, along with a recommendation regarding how to proceed based on the phenotype (and possible outcome). This will involve decision support at the point of care, to guide the clinician in safe prescribing. Clinician education regarding possible drug-gene or drug-drug interactions will also be necessary.

There are several ways to provide information to facilitate use by the provider treating the patient. Information about the patient's phenotype can be provided, along with guidance for use. This can be in the form of a formal pharmacogenomics consultation note; in some settings this could take the form of an entry into the patient's Problem List, or even information in the form of a letter, which in addition to being documented in the chart could be given to the patient, and made available to other relevant providers. Alerts can be programmed into the EHR that will provide information to the provider, either at the beginning of the patient encounter, or at the moment of drug prescribing. As discussed above, giving the provider information prior to the decision about drug choice and discussion with the patient leads to more provider willingness to consider recommendations and to change the plan.[38]

Consideration should be given to providing this sort of "passive interpretive" Clinical Decision Support (CDS) in the EHR, which could be viewed at the beginning of the patient encounter. Clinical guidelines such as those by CPIC will need to be utilized to inform prescribing recommendations. Other features in addition to the patient's phenotype and its significance that should likely be included in CDS are: recommendations for dosing changes; need for monitoring; alternative drug recommendations; and patient education recommendations. A combination of passive information and active alerts is expected to be the optimal way support the provider. In the presence of pharmacogenomic information, the flow of the patient encounter and decision making regarding drug prescribing is diagrammed below in figure 3.

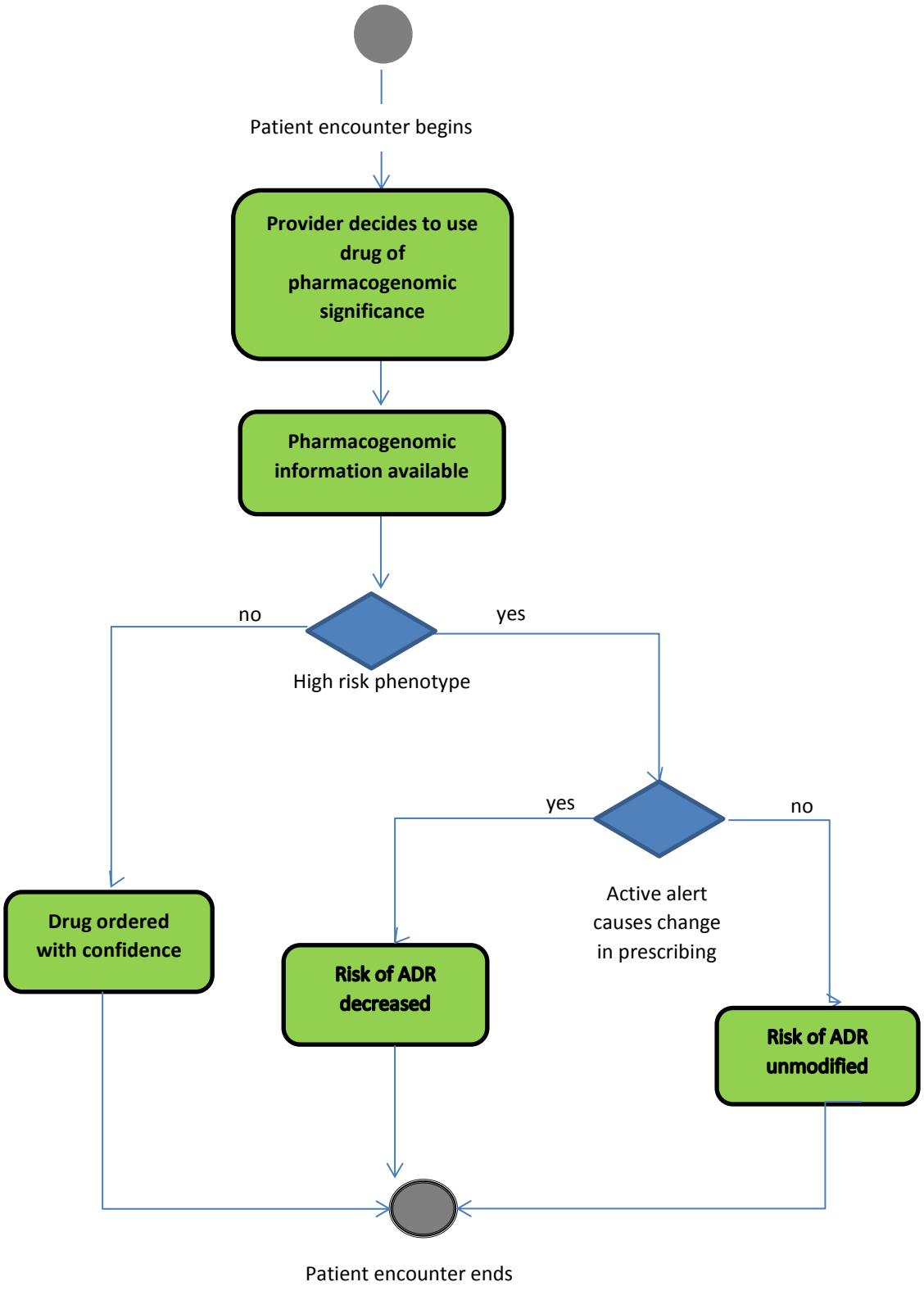

FIGURE 3: PROPOSED MODEL OF PHARMACOGENOMIC-BASED PRESCRIBING WITH ACTIVE\INTERRUPTIVE ALERTS.

Implementation of the reporting and subsequent use of pharmacogenomic variants of significance will take a multistep process, and require leadership and buy-in to optimize implementation. The following necessary steps have been described to successfully implement preemptive Pharmacogenomics testing based on experience at St. Jude Children's Hospital.[15] First, there must be a standard way of getting testing result information into the EHR. There must be a permissive institutional environment including both infrastructure and technical support. There must also be an overseeing body which determines which test results are part of the EHR, and which drug-gene pairs are linked to active-interruptive alerts. There must be a process for keeping abreast of pharmacogenomic knowledge as the field advances, and this knowledge must be used in a standard process to update tests and clinical recommendations as the knowledge base expands.

In addition to leadership support, implementation teams and stakeholders need to work collaboratively. Such stakeholders will include clinical informatics and bioinformatics experts, providers (both specialists such as genetic counselors and geneticists, and generalists), pharmacists, information security and privacy personnel, and laboratorians.

The process of developing the EHR interface and CDS content will need to involve users, decision makers, and evaluators. The users will need to be asked about the tasks they do on a daily basis to provide patient care, and about the clinical decisions that would benefit from computer decision support.

Stakeholder/users should be surveyed to find out their needs, by asking questions in the following areas:

1. What information do you need that you don't have?
2. Where in the EHR would pharmacogenomic information be located? Would a link-out to a curated definitive information source help? Or would you prefer a more concise summary linked to the moment of prescribing? Or both?
3. How will you decide which drugs-gene pairs to implement alerts for in the EHR?
4. What process will be used to update the system? Who will be responsible?

5. How will new genomic results be put into the EHR, and converted to phenotypes with defined actions?
6. Who will make sure that the pharmacogenomic actions are kept up to date with the rapidly advancing field?
7. What do you want the CDS tool to look like? What level of alerts do you want to see? Do you want to be able to ignore an alert?
8. Who will be responsible for monitoring the use of the alerts, and modifying ones which get ignored frequently?

Once the needs of the providers and stakeholders have been identified, the CDS interface will be designed. This will focus on the formatting and usability of the alerts and reminders, as it will likely be an add-on to an existing EHR platform with other types of alerts. The targeted users will be shown the interface, and asked how to better integrate the pharmacogenomic knowledge base into the clinical work flow.

There is a growing body of literature to inform the use of CDS. As described by Kannry et al, the elements of a successful implementation and use of CDS include: [40]

1. active and actionable decision support,
2. multiple rounds of usability testing with iterative development for user acceptance,
3. numerous workflow events that result in CDS assistance,
4. dedicated training and support for users of the CDS tool for user adoption, and
5. support from clinical and administrative leadership.

Frequent, unimportant alerts can distract clinicians, and limit the effectiveness of CDS. One way to minimize this is to consider what information needs to be brought to the clinician's attention as an "interruptive" alert, and what information can be presented more informatively. Color and font can be used to portray the importance of the alert, and the level of user input needed to dismiss the alert can vary with the danger posed by overriding the alert. The alert should include relevant patient data in the context of the alert and allowing clinicians to respond with one or two clicks. [41] Typing in response to the

alert should be kept at a minimum, especially if no one is reviewing the typed input. It is important to put the information at the right point in the workflow, so that it is easily actionable.

Horsky et al have made the following design recommendations for alerts and reminders for use in prescribing CDS [42]:

1. Tiered severity level: real-time, interruptive alerts should be reserved only for high severity warnings.
2. Concise text with justification: content should be limited to 1-2 lines, with a brief justification separated visually.
3. Clear response options: buttons with simple labels (order or cancel), with action links to possible alternate options.
4. Concurrent alert priority: prioritize multiple alerts for a single order, with high-severity alerts emphasized.
5. Unobtrusive reminders: for lower severity alerts, use flags or color-coded messages in reserved screen areas.
6. Meaningful use of color: 5-6 colors at most to maintain emphasis, which correlate to risk across different scenarios. Can use color shades for gradients.
7. Text luminosity: high contrast ratio with dark text on light background; match color pairs if needed.
8. Filtering rules: evaluate triggers to increase specificity and limit “false positives”.
9. Curate and revise trigger rules: periodic reviews by a committee of frequently overridden alerts.
10. Prompt for EHR edits: include a link to edit and update allergy and medication lists for alerts that are frequently overridden.

A mock-up of the EHR and CDS interface should be designed based on these principles. Two types of alerts should be used: one should be a warning, which gives strong advice to stop before ordering the drug, with a clearly specified reason (based on high risk phenotype being present). The other should be more informative, with options for safe prescribing which may include further monitoring. Links directly to order sets should be provided so that the task of being cautious and following practice guidelines is made easy for the provider while reducing cognitive load. The following are examples of

formatting for less and more serious alerts, with actions made simple by the use of order buttons integrated into the alerts.

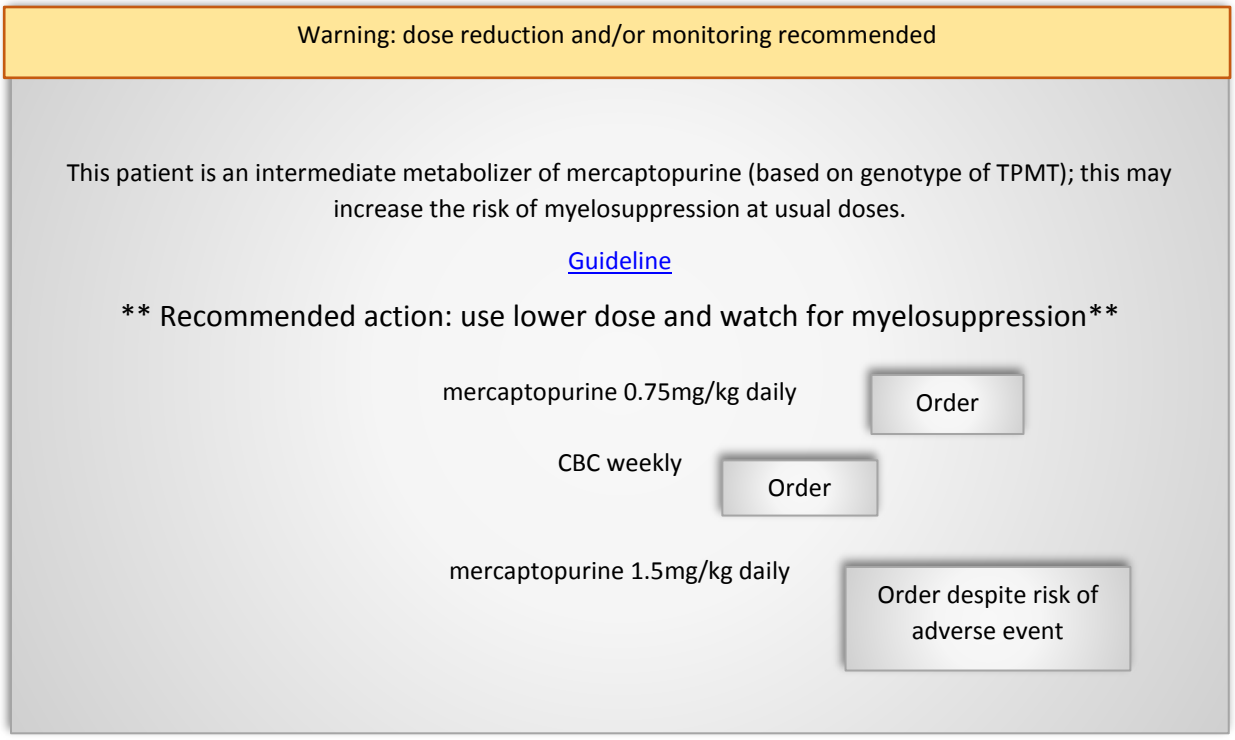

FIGURE 4: MOCK UP FOR CHANGE IN PRESCRIBING

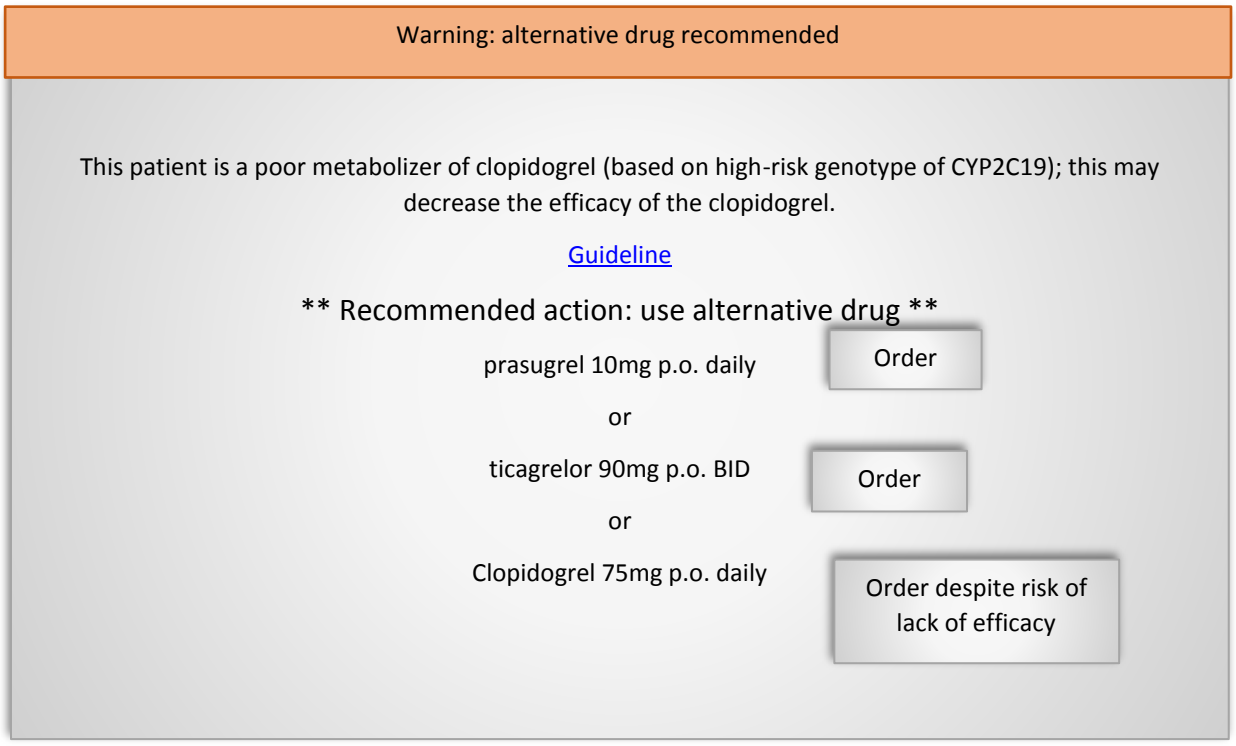

FIGURE 5: MOCK-UP FOR ACTIVE INTERRUPTIVE ALERT

Once the interface for the Electronic Health Records has been designed, it should be tested on a small group of users. A useful way of performing usability testing is to use the Post-Study System Usability Questionnaire (PSSUQ). [See Appendix H.] This is a 19 item scale that was initially developed for use at IBM to evaluate computer system usability; it has also been called the CSUQ (Computer System Usability Questionnaire).[43] PSSUQ asks questions in five domains that are designed to assess the usability characteristics of the system: quick completion of work, ease of learning, high-quality documentation, functional task adequacy, and rapid acquisition of usability expertise for the system. Further studies of the psychometric features of the PSSUQ reveal that is comprised of a 3-factor structure (System Usefulness, Information Quality, and Interface Quality), and has significant generalizability over time and for different types of systems.[44]

In addition to assessing the usability with the PSSUQ, evidence of ways the system is being utilized will be evaluated for needed changes. Often PGx implementation into EHR will be based on either guidelines or protocols. In the case of guidelines, the level of adherence may need to be measured.

Such guidelines may come from CPIC, or from a particular institutional committee or other organization. For protocols, the level of compliance may need to be measured. In regard to protocols, a specific clinical algorithm is implemented which then alters the path of care for the patient. In this latter case integration into the EHR is critically important to keep track of both care quality and performance.

The generation of alerts can be tracked, as can the use of provider overrides with medication prescribing. If certain alerts are routinely ignored, these can be eliminated or changed to make sure they are relevant. The use of the passive interpretive information can also be monitored, although the depth of understanding gained from this task or application to practice change will be less clear. Some examples of process measures are listed in table 8 and some examples of outcome measures are listed in table 9.

Examples of Process Measures
Was PGx data available in EHR?
PGx information in EHR reviewed prior to prescribing?
How often was warning overridden?
Recommended genotyping obtained prior to prescribing?

TABLE 9: EXAMPLES OF PROCESS MEASURES

Examples of Outcome Measures
Number of drug related ADR in when warnings overridden
Number of drug related ADRs when recommended testing not obtained
Number of drug related ADRs when recommended alternate drugs or alternate dosing used

TABLE 10: EXAMPLES OF OUTCOME MEASURES

CHAPTER 6: DISCUSSION

This analysis has provided several results that require thoughtful interpretation to be meaningful, to help advance the understanding of pharmacogenomics, and to guide future research efforts. There are also important implications for implementation within the healthcare system. The ANNS for both the CUMC data set and NCGENES data set were found to be fairly similar: 46 and 54 respectively. However, they are an order of magnitude different from the approximation from the general population. There are several possible explanations for these differences. It is possible that the differences between the CUMC and NCGENES data sets are the due to a difference in the ethnic composition of the patients whose exomes are represented in the data sets; some genotypes and phenotypes are more common in certain races (i.e. G6PD deficiency in those of African origin); thus the location of the facility where the WES was done and the population in that catchment area may explain some of the difference in the ANNS results. However, it is unlikely that the population in either of these data sets was different enough from the general population to result in an order of magnitude in difference as compared to projections from available population data. It is much more plausible that this difference is a consequence of the use of WES incidental findings to identify pharmacogenomically relevant variants with existing diagnostic WES bioinformatics pipelines rather than optimized methods for determining the presence of pharmacogenomics variants.

Some of the limitations that were recognized during this work include the impracticality of determining the phase of multiple variants occurring within the same gene, a frequent occurrence in some common pharmacogenes. For example, while there are many pharmacogenomic variants of significance in the CYP2D6 gene, the CYP2D6 data could not be used for either of these sets of experimental data because it was not possible to determine the phase of compound variants which are particularly relevant

in CYP2D6. If the CYP2D6 data had been technically feasible to include (for example, by the use of a technique other than WES) the ANNS would have been even lower.

In addition to the above limitations in the use of WES, other technical issues such as the use of primer sets, and bioinformatics pipelines that were not optimized to make accurate calls regarding these pharmacogenetic variants, makes the use of WES less than optimal and may have contributed further to the difference between our calculations based on the NCGENES and CUMC data and projections from population data. Certainly other approaches are well developed and exist, which can determine such variant alleles and other complex constructs, however, they are typically special purpose and do not provide for exploitation of incidental findings. Another technology which is in its infancy which has some similarities with whole exome sequencing but which may permit the discrimination of phase in variant calls is whole genome sequencing.

An initial goal was to determine if an aggregate number needed to screen per serious adverse event prevented could be computed. Unfortunately, much of the literature and the PharmGKB knowledge base have focused on the question of evidence for an effect, not on the size or severity of the effect. Hence for many such adverse events the magnitude of the rate of the adverse reactions is not readily available in the literature. Therefore, the focus of the data analysis was on “actionable” variants rather than being stratified by severity. Hence the number needed to screen to prevent an adverse event is expected to be much higher than the ANNS for clinical impact.

It is also worth noting that, although there is utility in using WES for pharmacogenomics data if they are available, only a small (though growing) number of patients at most medical centers undergo such testing. Thus WES is not expected to be a viable source of pharmacogenomic information for many patients presently. However, in the future the number of WES results may increase, and in addition other technologies such as whole genome sequencing will probably become more prevalent and make implementation of pharmacogenomic results into patient care more feasible and likely to occur.

Indeed it is most likely that an effort to implement reporting of pharmacogenomic findings from WES alone would not be compelling. However, as genomic based analysis becomes more common, and

pharmacogenomics testing using a variety of methods and models become more common, all of these pharmacogenomically relevant data will need to be effectively integrated into patient care.

The challenge of integrating knowledge into healthcare systems is well recognized in general. In the 2007 Workshop summarized in "The Learning Healthcare System" the IOM Roundtable on Evidence-Based Medicine depicted their vision for a learning healthcare system in which "evidence is both applied and developed as a natural product of the care process."[45] However, they noted the need for expanded ability to produce such evidence to support medical care. Nowhere is this likely to be truer than in implementing pharmacogenomics in such "learning healthcare systems." The model implementation plan proposed herein may form a backbone for creating such a system from a pharmacogenomics perspective.

CHAPTER 7: CONCLUSION

There are a variety of lessons with general applicability that this analysis provides. First, based on this analysis the pharmacogenomically relevant impact of WES based incidental screening is in the range of 46 to 52 persons needed to screen, even when using incidental findings from non-optimized WES. When using a very sensitive test this number is expected to be very low, corresponding to an ANNS of 5. This suggests that if such data were available that they could be quite useful in caring for patients. It should be recalled, however, that this is the number needed to screen for a clinically relevant change in care, not the number to prevent an adverse event. This latter number is expected to be much higher.

Pharmacogenomics has the potential to impact the care of large numbers of patients currently receiving care within the US healthcare system. Although WES has significant limitations when applied to pharmacogenomics, even when these are considered the expected aggregate number needed to screen is in the range of 46 to 52 for our data sets. The use of whole genome sequencing in the future could make incidental pharmacogenomics findings more robust, and the aggregate number needed to screen may drop significantly. However, it is worth noting that WES or WGS are unlikely to be performed on a large percentage of the patient population at any medical center for the foreseeable future. Pharmacogenomic information may be valuable enough that specific pre-emptive pharmacogenomics screening panels (likely to be array based) may be a much more common source of pharmacogenomic information.

APPENDIX A— LIST OF DRUGS WITH PHARMACOGENOMICS ON THE FDA LABEL

Drug	PHARMACOGENOMICS on FDA label	FDA Label Excerpt
Abacavir **CPIC A** **PharmGKB 1A** **Dutch guideline**	Genetic testing required	All patients should be screened for the HLA-BCPIC A5701 allele prior to initiating therapy with ZIAGEN or reinitiation of therapy with ZIAGEN, unless patients have a previously documented HLA-BCPIC A5701 allele assessment. Patients who carry the HLA-BCPIC A5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-BCPIC A5701 allele. ZIAGEN is contraindicated in patients: who have the HLA-BCPIC A5701 allele.
Allopurinol **CPIC A** **PharmGKB 1A**	none	
Amitriptyline **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers")...Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses...In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers...It is desirable to monitor TCA plasma levels whenever a TCA is going to be coadministered with another drug known to be an inhibitor of P450 2D6.
aripiprazole **CPIC B** **Dutch guideline**	Actionable Pharmacogenomics	Dosing recommendation in patients who are classified as CYP2D6 poor metabolizers (PM): The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response. The dose of aripiprazole for PM patients who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose. Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose to one-half of the usual dose when used concomitantly (2.6, 7.1), except when used as adjunctive treatment with antidepressants CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly
atomoxetine **CPIC B** **Dutch guideline** **PharmGKB 2A**	Actionable Pharmacogenomics	Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and Css,max is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent

		inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity (extensive metabolizers (EMs)). Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure. In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and Css,max is about 3- to 4-fold greater than atomoxetine alone. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.
Azathioprine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Genetic testing recommended	Patients with intermediate thiopurine S-methyl transferase (TPMT) activity may be at an increased risk of myelotoxicity if receiving conventional doses of IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of IMURAN. TPMT genotyping or phenotyping can help identify patients who are at an increased risk for developing IMURAN toxicity TPMT Testing: It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMTCPIC A2, TPMTCPIC A3A and TPMTCPIC A3C. Patients with two nonfunctional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable. TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING IMURAN. See CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections. One of the pathways for inactivation of azathioprine is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concomitantly should have a dose reduction of IMURAN, to approximately 1/3 to 1/4 the usual dose. It is recommended that a further dose reduction or alternative therapies be considered

		for patients with low or absent TPMT activity receiving IMURAN and allopurinol because both TPMT and XO inactivation pathways are affected.
Capecitabin CPIC A PharmGKB 1A Dutch guideline	Actionable Pharmacogenomics	Increased Risk of Severe or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity: Withhold or permanently discontinue XELODA in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No XELODA dose has been proven safe in patients with absent DPD activity. Based on post-marketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA.
Carbamazepine CPIC A PharmGKB 1A	Genetic testing required	Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-BCPIC A1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity. Across Asian populations, notable variation exists in the prevalence of HLA-BCPIC A1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-BCPIC A1502, averaging 2 to 4%, but higher in some groups. HLA-BCPIC A1502 is present in <1% of the population in Japan and Korea. HLA-BCPIC A1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). Prior to initiating Tegretol therapy, testing for HLA-BCPIC A1502 should be performed in patients with ancestry in populations in which HLA-BCPIC A1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLABCPIC A1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Tegretol should not be used in patients positive for HLABCPIC A1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN. Over 90% of Tegretol treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at risk patients currently on Tegretol.

Celecoxib **CPIC B** **PharmGKB 2A** **NO guideline**	Actionable Pharmacogenomics	Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers. Consider using alternative management in JRA patients who are poor metabolizers. Celecoxib metabolism is primarily mediated via CYP2C9. CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9CPIC A2 and CYP2C9CPIC A3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9CPIC A3/CPIC A3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9CPIC A1/CPIC A1 or CPIC AI/CPIC A3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as CPIC A2, CPIC A5, CPIC A6, CPIC A9 and CPIC A11. It is estimated that the frequency of the homozygous CPIC A3/CPIC A3 genotype is 0.3% to 1.0% in various ethnic groups. Consider a dose reduction by 50% (or alternative management for JRA) in patients who are known or suspected to be CYP2C9 poor metabolizers.
Chloroquine **CPIC B** **PharmGKB 3** **NO guideline**	Actionable Pharmacogenomics	Hematological Effects/Laboratory Tests Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered. The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency.
Citalopram **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. In vitro studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the TCA imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCAs with Celexa.
Clobazam **CPIC C** **PharmGKB 2A**	Actionable Pharmacogenomics	Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, the initial dose in patients known to be CYP2C19 poor metabolizers should be 5 mg/day. These patients should be titrated initially to 10-20 mg/day, and may be titrated further to a maximum daily dose of

		40 mg if tolerated...In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in urine than in CYP2C19 extensive metabolizers.
Clomipramine **CPIC A and B** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6...is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers...It is desirable to monitor TCA plasma levels whenever an agent of the tricyclic antidepressant class including Anafranil is going to be co-administered with another drug known to be an inhibitor of P450 2D6...
Clopidogrel **CPIC A** **PharmGKB 1A** **Dutch guideline**	Genetic testing recommended	The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19...Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternate treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.
Clozapine **CPIC C**	Actionable Pharmacogenomics	Dose reduction may be necessary in patients who are CYP2D6 poor metabolizers. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted. A subset (3%–10%) of the population has reduced activity of CYP2D6 (CYP2D6 poor metabolizers). These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. Concomitant use of CLOZARIL with other drugs metabolized by CYP2D6 can increase levels of these CYPD26 substrates. Use caution when coadministering CLOZARIL with other drugs that are metabolized by CYP2D6. It may be necessary to use lower doses of such drugs than usually prescribed. Such drugs include specific antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide).
Codeine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6CPIC A2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at

		labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Codeine is secreted into human milk...some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.
Dabrafenib **CPIC B/C**	Actionable PHARMACOGENOMICS	TAFINLAR, which contains a sulfonamide moeity, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.
Dapsone **CPIC B** **PharmGKB 1b** **NO guideline**	Actionable Pharmacogenomics	Oral dapsone treatment has produced dose-related hemolysis and hemolytic anemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more prone to hemolysis with the use of certain drugs...There was no evidence of clinically relevant hemolysis or anemia in patients treated with ACZONE Gel, 5%, including patients who were G6PD deficient. Some subjects with G6PD deficiency using ACZONE Gel developed laboratory changes suggestive of mild hemolysis. WARNINGS AND PRECAUTIONS Hematological Effects: Some subjects with G6PD deficiency using ACZONE Gel developed laboratory changes suggestive of mild hemolysis. (5.1)(8.6)
Desipramine **CPIC A** **PharmGKB 1A**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6...is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers...It is desirable to monitor TCA plasma levels whenever a TCA including is going to be co-administered with another drug known to be an inhibitor of P450 2D6.
Dexlansoprazole **CPIC B**	Actionable Pharmacogenomics	In male Japanese subjects who received a single dose of DEXILANT 30 mg or 60 mg (N=2 to 6 subjects/group), mean dexlansoprazole Cmax and AUC values were up to 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean Cmax was up to 4 times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Though such study was not conducted in Caucasians and African Americans, it is expected dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well. Concomitant administration of

		dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.
Diazepam CPIC C PharmGKB 3	Actionable Pharmacogenomics	The metabolism of diazepam...involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4)...The marked inter-individual variability in clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19...and CYP3A4.
Doxepin CPIC A PharmGKB 1A/3 Dutch guideline	Actionable Pharmacogenomics	Silenor is primarily metabolized by hepatic cytochrome P450 isozymes CYP2C19 and CYP2D6, and to a lesser extent, by CYP1A2 and CYP2C9. Inhibitors of these isozymes may increase the exposure of doxepin. Since doxepin is metabolized by CYP2C19 and CYP2D6, inhibitors of these CYP isozymes may increase the exposure of doxepin. ...A maximum dose of doxepin in adults and elderly should be 3 mg, when doxepin is co-administered with cimetidine. Poor metabolizers of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
Escitalopram CPIC A PharmGKB 1A	None	
esomeprazole CPIC B PharmGKB 3 Dutch guideline	Actionable Pharmacogenomics	CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole...At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.
Fluorouracil CPIC A PharmGKB 1A Dutch guideline	Actionable Pharmacogenomics	Excerpts from the Carac drug label: Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop. Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase 'DPD' activity. One case of life-threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity... Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil. Excerpts from the Adrucil drug label: Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this

		catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.
Fluvoxamine **CPIC A** **PharmGKB 1A**	Informative Pharmacogenomics	Based on a finding of substantial interactions of fluvoxamine with certain of these drugs... and limited in vitro data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of others drugs such as: CYP1A2 (e.g., warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g., warfarin), CYP3A4 (e.g., alprazolam), and CYP2C19 (e.g.,omeprazole). In vitro data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).
Glibenclamide **CPIC B** **PharmGKB 3**	Actionable Pharmacogenomics	Hemolytic Anemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLYNASE PresTab belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
Glimepiride **CPIC B**	Actionable Pharmacogenomics	Hemolytic Anemia: Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because AMARYL is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative.
Glipizide **CPIC B**	Actionable Pharmacogenomics	Hemolytic Anemia: Treatment of patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because GLUCOTROL belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered.
Iloperidone **CPIC B/C** **PharmGKB 3**	Actionable Pharmacogenomics	The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26 and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. Co-administration of FANAPT with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3 fold increase in iloperidone plasma exposure, and therefore one-half of the FANAPT dose should be administered. Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs and PMs should have their dose reduced by one half. Laboratory tests are available to identify CYP2D6 PMs. FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, FANAPT dose should be increased to where it was before.

Imipramine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so-called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug.
irinotecan **CPIC A** **PharmGKB 2A** **Dutch guideline**	Actionable Pharmacogenomics	Individuals who are homozygous for the UGT1A1CPIC A28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment...When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1CPIC A28 allele.
Ivacaftor **CPIC A** **PharmGKB 1A**	Genetic testing required	KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. KALYDECO is indicated for the treatment of CF in patients age 2 years and older who have an R117H mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bidirectional sequencing when recommended by the mutation test instructions for use. Limitations of Use: Not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene.
Mafenide **CPIC B**	Actionable Pharmacogenomics	Fatal hemolytic anemia with disseminated intravascular coagulation, presumably related to a glucose-6-phosphate dehydrogenase deficiency, has been reported following therapy with SULFAMYLON Cream.
Mercaptopurine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Genetic testing recommended	Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP. TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or

		intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. Homozygous-deficient patients (two non-functional alleles), if given usual doses of mercaptopurine, accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to PURINETHOL toxicity (see WARNINGS and PRECAUTIONS). Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity (see WARNINGS and PRECAUTIONS). TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity. If a patient has clinical or laboratory evidence of severe bone marrow toxicity, particularly myelosuppression, TPMT testing should be considered.
methylene blue **CPIC B** **PharmGKB 3**	Actionable Pharmacogenomics	Methylene blue should be avoided in patients with G6PD deficiency due to the risk of paradoxical methemoglobinemia and hemolysis.
Metoclopramide **CPIC D**	Actionable Pharmacogenomics	Patients with NADH-cytochrome b5 reductase deficiency are at an increased risk of developing methemoglobinemia and/or sulfhemoglobinemia when metoclopramide is administered. ...neonates have reduced levels of NADH-cytochrome b5 reductase which, in combination with the aforementioned pharmacokinetic factors, make neonates more susceptible to methemoglobinemia.
Nalidixic acid **CPIC B**	Actionable Pharmacogenomics	Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. ADVERSE REACTIONS...Other: Tendon disorders including tendon rupture, cholestasis, paresthesia, metabolic acidosis, thrombocytopenia, leukopenia, or hemolytic anemia, sometimes associated with glucose 6-phosphate dehydrogenase deficiency and peripheral neuropathy.
Nilotinib **CPIC C** **PharmGKB 3**	Genetic Testing required	Tasigna can increase bilirubin levels. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during Tasigna treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. However, the largest increases in bilirubin were observed in the (TA)7/(TA)7 genotype (UGT1A1*28) patients.
Nitrofurantoin **CPIC B** **PharmGKB C** **NO guideline**	Actionable Pharmacogenomics	Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing Furadantin; hemolysis ceases when the drug is withdrawn.
Norfloxacin **CPIC B** **NO guideline**	Actionable Pharmacogenomics	Rarely, hemolytic reactions have been reported in patients with latent or actual defects in glucose-6-phosphate dehydrogenase

		activity who take quinolone antibacterial agents, including norfloxacin (see ADVERSE REACTIONS). Adverse Reactions...Hematologic: Neutropenia; leukopenia; agranulocytosis; hemolytic anemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency; thrombocytopenia.
Nortriptyline **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P4502D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called 'poor metabolizers'); reliable estimates of the prevalence of reduced P4502D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics propafenone and flecainide).
Oxycodone **CPIC A** **PharmGKB 2A**	none	
Pantoprozole **CPIC B** **PharmGKB 3**	Actionable Pharmacogenomics	Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In in vivo drug-drug interaction studies with CYP2C19 substrates (diazepam (also a CYP3A4 substrate) and phenytoin (also a CYP3A4 inducer) and clopidogrel), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates), and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed. Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers. For known pediatric poor metabolizers, a dose reduction should be considered.
Paroxetine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Informative Pharmacogenomics	The metabolism of paroxetine is accomplished in part by cytochrome CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions. In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6.

		Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine. Therefore, coadministration of paroxetine hydrochloride with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, tamoxifen and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution. However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine, and thioridazine should not be coadministered. Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and hence reduced efficacy of tamoxifen.
Pazopanib **CPIC B/C**	Actionable Pharmacogenomics	Pazopanib can increase serum total bilirubin levels...In vitro studies showed that pazopanib inhibits UGT1A1, which glucuronidates bilirubin for elimination. In [a pooled pharmacogenetic] analysis, the (TA)7/(TA)7 genotype (UGT1A1*28/*28) (underlying genetic susceptibility to Gilbert's syndrome) was associated with a statistically significant increase in the incidence of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes. If ALT elevations >3 X ULN occur concurrently with bilirubin elevations > 2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (uncojugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome...Patients with only a mild indirect hyperbilirubinemia, known as Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations.
Peginterferon alfa-2a **CPIC A** **PharmGKB 1A**	None	
peginterferon alfa-2b **CPIC A** **PharmGKB 1A**	Actionable Pharmacogenomics	When administering PegIntron with medications metabolized by CYP2C8/9 (e.g., warfarin and phenytoin) or CYP2D6 (e.g., flecainide), the therapeutic effect of these substrates may be decreased. A retrospective genome-wide association analysis1,2 of 1,671 subjects (1,604 subjects from Study 4 and 67 subjects from another clinical trial) was performed to identify human genetic contributions to anti-HCV treatment response in previously untreated HCV genotype 1 subjects. A single nucleotide polymorphism near the gene encoding interferon-lambda-3

		(IL28B rs12979860) was associated with variable SVR rates. The rs12979860 genotype was categorized as CC, CT and TT. In the pooled analysis of Caucasian, African-American, and Hispanic subjects from these trials (n=1,587), SVR rates by rs12979860 genotype were as follows: CC 66% vs. CT 30% vs. TT 22%. The genotype frequencies differed depending on racial/ethnic background, but the relationship of SVR to IL28B genotype was consistent across various racial/ethnic groups (see Table 12). Other variants near the IL28B gene (e.g., rs8099917 and rs8103142) have been identified; however, they have not been shown to independently influence SVR rates during treatment with pegylated interferon alpha therapies combined with ribavirin
Pegloticase **CPIC B** **PharmGKB 3**	Genetic testing recommended	Patients deficient in G6PD have reduced ability to reduce the hydrogen peroxide formed as a major byproduct of the pegloticase-catalyzed oxidation of uric acid to allantoin. Excerpt from the pegloticase *(KRYSTEXXA)* drug label: Before starting KRYSTEXXA, patients at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia.
Perphenazine **CPIC B/C**	Actionable Pharmacogenomics	The pharmacokinetics of perphenazine covary with the hydroxylation of debrisoquine which is mediated by cytochrome P4502D6 (CYP2D6) and thus is subject to genetic polymorphism, i.e., 7%-10% of Caucasians and a low percentage of Asians have little or no activity and are called "poor metabolizers". Poor metabolizers of CYP2D6 will metabolize perphenazine more slowly and will experience higher concentrations compared with normal or "extensive" metabolizers. Poor metabolizers demonstrate higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events. The concomitant administration of other drugs that inhibit the activity of P4502D6 may acutely increase plasma concentrations of antipsychotics. Among these are tricyclic antidepressants and selective serotonin reuptake inhibitors, e.g., fluoxetine, sertraline and paroxetine. When prescribing these drugs to patients already receiving antipsychotic therapy, close monitoring is essential and dose reduction may become necessary to avoid toxicity. Lower doses than usually prescribed for either the antipsychotic or the other drug may be required.
Phenytoin **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. Phenytoin is metabolized by hepatic cytochrome P450 enzymes CYP2C9 and CYP2C19, and is particularly susceptible to inhibitory drug interactions because it is subject to saturable

		metabolism. Inhibition of metabolism may produce significant increases in circulating phenytoin concentrations and enhance the risk of drug toxicity. Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-BCPIC A1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLABCPIC A1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-BCPIC A1502.
Pimozide **CPIC B** **PharmGKB 4**	Genetic testing required	Individuals with genetic variations resulting in poor CYP2D6 metabolism (approximately 5 to 10% of the population) exhibit higher pimozide concentrations than extensive CYP2D6 metabolizers. The concentrations observed in poor CYP 2D6 metabolizers are similar to those seen with strong CYP2D6 inhibitors such as paroxetine. The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP2D6 metabolizers because of the prolonged half-life. Alternative dosing strategies are recommended in patients who are genetically poor CYP2D6 metabolizers. In children: At doses above 0.05mg/kg/day, CYP2D6 genotyping should be performed. In poor CYP2D6 metabolizers, ORAP doses should not exceed 0.05mg/kg/day, and doses should not be increased earlier than 14 days. In adults: At doses above 4 mg/day, CYP2D6 genotyping should be performed. In poor CYP2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days.
Primaquine **CPIC B** **PharmGKB 3**	Actionable Pharmacogenomics	If primaquine phosphate is prescribed for (1) an individual who has shown a previous idiosyncrasy to primaquine phosphate (as manifested by hemolytic anemia, methemoglobinemia, or leukopenia), (2) an individual with a family or personal history of favism, or (3) an individual with erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or nicotinamide adenine dinucleotide (NADH) methemoglobin reductase deficiency, the person should be observed closely for tolerance. The drug should be discontinued immediately if marked darkening of the urine or sudden decrease in hemoglobin concentration or leukocyte count occurs.
Probenecid **CPIC B**	Actionable Pharmacogenomics	Hematologic: aplastic anemia, leukopenia, hemolytic anemia which in some patients could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells, anemia.
Propafenone **CPIC C** **PharmGKB 2A**	Actionable Pharmacogenomics	Propafenone is metabolized by CYP2D6,CYP3A4,and CYP1A2 isoenzymes. Approximately 6% of Caucasians in the U.S. population are naturally deficient in CYP2D6 activity and to a somewhat lesser extent in other demographic groups. Drugs

		that inhibit these CYP pathways(such as desipramine,paroxetine,ritonavir,sertraline for CYP2D6; ketoconazole, erythromycin, saquinavir, and grapefruit juice for CYP3A4; and amiodarone and tobacco smoke for CYP1A2) can be expected to cause increased plasma levels of propafenone. Increased exposure to propafenone may lead to cardiac arrhythmias and exaggerated beta-adrenergic blocking activity. Because of its metabolism, the combination of CYP3A4 inhibition and either CYP2D6 deficiency or CYP2D6 inhibition in users of propafenone is potentially hazardous. Therefore, avoid simultaneous use of propafenone ER capsules with both a CYP2D6 inhibitor and a CYP3A4 inhibitor. There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed.
Protriptyline **CPIC B**	Actionable Pharmacogenomics	The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"). Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the Type 1C antiarrhythmics, propafenone and flecainide).
Quinine **CPIC B**	Actionable Pharmacogenomics	QUALAQUIN is contraindicated in patients with the following: Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Hemolysis can occur in patients with G6PD deficiency receiving quinine. Desipramine (CYP2D6 susbtrate): Quinine (750 mg/day for 2 days) decreased the metabolism of desipramine in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers.
Rasburicase **CPIC A** **PharmGKB 1A**	Genetic testing required	Do not administer Elitek to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Immediately and permanently discontinue Elitek in patients developing hemolysis. Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek. Elitek is contraindicated in patients with G6PD deficiency because hydrogen peroxide is one of the major by-products of the conversion of uric acid to allantoin. In clinical studies,

		hemolysis occurs in <1% patients receiving Elitek; severe hemolytic reactions occurred within 2-4 days of the start of Elitek. Immediately and permanently discontinue Elitek administration in any patient developing hemolysis. Institute appropriate patient monitoring and support measures (e.g., transfusion support). Screen patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) prior to starting Elitek. It is not known whether patients with deficiency of cytochrome b5 reductase (formerly known as methemoglobin reductase) or of other enzymes with antioxidant activity are at increased risk for methemoglobinemia or hemolytic anemia.
Ribavirin **CPIC A** **PharmGKB 1A**	None	
Sertraline **CPIC B** **PharmGKB 1A**	None	
Simvastatin **CPIC A** **PharmGKB 1A**	None	
Succinylcholine **CPIC B** **PharmGKB 3**	Actionable Pharmacogenomics	RISK OF CARDIAC ARREST FROM HYPERKALEMIC RHABDOMYOLYSIS There have been rare reports of acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death after the administration of succinylcholine to apparently healthy children who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne's muscular dystrophy. Succinylcholine is contraindicated in persons with personal or familial history of malignant hyperthermia, skeletal muscle myopathies, and known hypersensitivity to the drug. WARNINGS: SUCCINYLCHOLINE IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE. Patients homozygous for atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine. In these patients, a 5- to 10-mg test dose of succinylcholine may be administered to evaluate sensitivity to succinylcholine, or neuromuscular blockade may be produced by the cautious administration of a 1-mg/mL solution of succinylcholine by slow IV infusion. Apnea or prolonged muscle paralysis should be treated with controlled respiration.
Sulfasalazine **CPIC B** **PharmGKB 4**	Actionable Pharmacogenomics	Patients with glucose-6 phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.
Tacrolimus **CPIC A** **PharmGKB 1A**	None	

Tamoxifen **CPIC A** **PharmGKB 2A**	None	
Tetrabenzine **CPIC C**	Genetic testing requiring	Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg. The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg. Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., fluoxetine, paroxetine) significantly increase the exposure to alpha-HTBZ and beta-HTBZ, therefore, the total dose of XENAZINE should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg.
Thioguanine **CPIC A** **PharmGKB 1A** **Dutch guideline**	Actionable Pharmacogenomics	There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. Prescribers should be aware that some laboratories offer testing for TPMT deficiency. Since bone marrow suppression may be associated with factors other than TPMT deficiency, TPMT testing may not identify all patients at risk for severe toxicity. Therefore, close monitoring of clinical and hematologic parameters is important. Bone marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.
Thioridazine **CPIC C** **PharmGKB 3**	Actionable Pharmacogenomics	Thioridazine is used to treat schizophrenic patients. It has potentially fatal effects on heart rhythm and should only be used if other antipsychotic drugs are not effective or cause intolerable side effects. Its use is warned against in people with reduced CYP2D6 activity and hence, reduced clearance of the drug, as that increases the likelihood of the potential fatal effects. Therefore, thioridazine is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6. Certain circumstances may increase the risk of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including 1) bradycardia, 2) hypokalemia, 3) concomitant use of other drugs that prolong the QTc interval, 4) presence of congenital prolongation of the QT interval, and 5) for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its coadministration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine.
tramadol **CPIC A** **PharmGKB 1B** **Dutch guideline**	Actionable Pharmacogenomics	Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are "poor metabolizers" of debrisoquine, dextromethorphan, tricyclic antidepressants, among other drugs. Based on a population PK

		analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers", while M1 concentrations were 40% lower. In vitro drug interaction studies in human liver microsomes indicates that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see WARNINGS) and serotonin syndrome.
Trimipramine **CPIC A** **PharmGKB 1A**	Actionable Pharmacogenomics	Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8 fold increase in plasma AUC of the TCA). Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug.
voriconazole **CPIC A** **PharmGKB 2A** **Dutch guideline**	Actionable Pharmacogenomics	Inhibitors and inducers of CYP3A4, CYP2C9, and CYP2C19 may alter VFEND concentrations. Adjust the VFEND dose and monitor for adverse events or lack of efficacy. VFEND may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce doses of and monitor for lack of efficacy or adverse events associated with drugs that are substrates of these enzymes. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 35%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCt) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.
Warfarin **CPIC A** **PharmGKB 1A**	Actionable Pharmacogenomics	The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose. Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration.

APPENDIX B – DRUGS WITH CPIC GUIDELINE INFORMATION

Drug	Guidelines (from www.pharmgkb.org/guidelines)	Updated
bacavir	CPIC CPIC Guideline for abacavir and HLA-B	*09/30/2014*
allopurinol	CPIC CPIC Guideline for allopurinol and HLA-B	*06/12/2015*
amitriptyline	CPIC CPIC Guideline for amitriptyline and CYP2C19,CYP2D6	*02/07/2014*
azathioprine	CPIC CPIC Guideline for azathioprine and TPMT	*05/10/2016*
capecitabine	CPIC CPIC Guideline for capecitabine and DPYD	*08/06/2014*
carbamazepine	CPIC CPIC Guideline for carbamazepine and HLA-B	*02/07/2014*
citalopram	CPIC CPIC Guideline for citalopram,escitalopram and CYP2C19	*05/11/2015*
clomipramine	CPIC CPIC Guideline for clomipramine and CYP2C19,CYP2D6	*02/07/2014*
clopidogrel	CPIC CPIC Guideline for clopidogrel and CYP2C19	*02/07/2014*
codeine	CPIC CPIC Guideline for codeine and CYP2D6	*05/05/2016*
desipramine	CPIC CPIC Guideline for desipramine and CYP2D6	*02/07/2014*
doxepin	CPIC CPIC Guideline for doxepin and CYP2C19,CYP2D6	*02/07/2014*
escitalopram	CPIC CPIC Guideline for citalopram,escitalopram and CYP2C19	*05/11/2015*
fluorouracil	CPIC CPIC Guideline for fluorouracil and DPYD	*07/30/2014*
fluvoxamine	CPIC CPIC Guideline for fluvoxamine and CYP2D6	*05/11/2015*
imipramine	CPIC CPIC Guideline for imipramine and CYP2C19,CYP2D6	*02/07/2014*
ivacaftor	CPIC CPIC Guideline for ivacaftor and CFTR	*05/16/2016*
mercaptopurine	CPIC CPIC Guideline for mercaptopurine and TPMT	*05/10/2016*
nortriptyline	CPIC CPIC Guideline for nortriptyline and CYP2D6	*02/07/2014*
paroxetine	CPIC CPIC Guideline for paroxetine and CYP2D6	*05/11/2015*
peginterferon alfa-2a	CPIC CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*02/25/2016*
peginterferon alfa-2b	CPIC CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*02/25/2016*
phenytoin	CPIC CPIC Guideline for phenytoin and CYP2C9,HLA-B	*02/03/2015*
rasburicase	CPIC CPIC Guideline for rasburicase and G6PD	*05/09/2014*
ribavirin	CPIC CPIC Guideline for peginterferon alfa-2a,peginterferon alfa-2b,ribavirin and IFNL3	*02/25/2016*
sertraline	CPIC CPIC Guideline for sertraline and CYP2C19	*05/11/2015*
simvastatin	CPIC CPIC Guideline for simvastatin and SLCO1B1	*06/30/2014*
tacrolimus	CPIC CPIC Guideline for tacrolimus and CYP3A5	*03/25/2015*
thioguanine	CPIC CPIC Guideline for thioguanine and TPMT	*05/10/2016*
trimipramine	CPIC CPIC Guideline for trimipramine and CYP2C19,CYP2D6	*02/07/2014*
warfarin	CPIC CPIC Guideline for warfarin and CYP2C9,VKORC1	*06/19/2014*

APPENDIX C – DRUG-GENE PAIRS, BASED ON THE LIST OF DRUGS IN APPENDIX A

Drugs	Genes
abacavir	HLA-B
allopurinol	HLA-B
amitriptyline	CYP2C19
amitriptyline	CYP2D6
aripiprazole	CYP2D6
atomoxetine	CYP2D6
azathioprine	TPMT
boceprevir	IFNL3
capecitabine	DPYD
carbamazepine	HLA-B
celecoxib	CYP2C9
chloroquine	G6PD
citalopram	CYP2C19
clomipramine	CYP2D6
clopidogrel	CYP2C19
clozapine	CYP2D6
codeine	CYP2D6
dapsone	G6PD
desipramine	CYP2D6
doxepin	CYP2C19
doxepin	CYP2D6
escitalopram	CYP2C19
esomeprazole	CYP2C19
fluorouracil	DPYD
fluvoxamine	CYP2D6
imipramine	CYP2C19
imipramine	CYP2D6
irinotecan	UGT1A1
ivacaftor	CFTR
mercaptopurine	TPMT
methylene blue	G6PD
nitrofurantoin	G6PD
norfloxacin	G6PD
nortriptyline	CYP2D6
oxycodone	CYP2D6
paroxetine	CYP2D6
peginterferon alfa-2a	IFNL3
peginterferon alfa-2b	IFNL3
phenytoin	CYP2C9
phenytoin	HLA-B

primaquine	G6PD
probenecid	G6PD
propafenone	CYP2D6
protriptyline	CYP2D6
rasburicase	G6PD
ribavirin	IFNL3
Selective serotonin reuptake inhibitors	CYP2C19
Selective serotonin reuptake inhibitors	CYP2D6
sertraline	CYP2C19
simvastatin	SLCO1B1
succinylcholine	RYR1
sulfasalazine	G6PD
tacrolimus	CYP3A5
tamoxifen	CYP2D6
telaprevir	IFNL3
tetrabenazine	CYP2D6
thioguanine	TPMT
thioridazine	CYP2D6
tramadol	CYP2D6
trimipramine	CYP2C19
trimipramine	CYP2D6
voriconazole	CYP2C19
warfarin	CYP2C9
warfarin	VKORC1

APPENDIX D – TABLES OF ALLELIC VARIANTS AND PREDICTED GENE FUNCTION

Allele	Allele2	Phenotype	Action	Drug	chance of drug exposure	phenotype frequency US population
CYP2C19*1	CYP2C19*17	UM	do not use	clomiprimine	0.000598587	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	escitalopram	0.040140272	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	citalopram	0.048015822	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	amitriptyline	0.019199168	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	imipramine	0.001382505	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	trimipramine	5.61573E-06	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	doxepin	0.00405065	0.0404634
CYP2C19*1	CYP2C19*2	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*3	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*4	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*5	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*6	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*7	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*8	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*1	CYP2C19*17	UM	do not use	desipramine	0.000369207	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	protriptyline	6.21277E-05	0.0404634
CYP2C19*1	CYP2C19*17	UM	do not use	nortriptyline	0.005517667	0.0404634
CYP2C19*1	CYP2C19*2	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*3	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*4	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*5	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*6	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*7	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*8	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*1	CYP2C19*17	UM	increase dose	esomeprazol	0.01780649	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	clomiprimine	0.000598587	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	escitalopram	0.040140272	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	citalopram	0.048015822	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	amitriptyline	0.019199168	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	imipramine	0.001382505	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	trimipramine	5.61573E-06	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	doxepin	0.00405065	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	desipramine	0.000369207	0.0404634
CYP2C19*17	CYP2C19*17	UM	do not use	protriptyline	6.21277E-05	0.0404634

CYP2C19*17	CYP2C19*17	UM	do not use	nortriptyline	0.005517667	0.0404634
CYP2C19*17	CYP2C19*17	UM	increase dose	esomeprazole	0.01780649	0.0404634
CYP2C19*2	CYP2C19*2	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	clomiprimine	0.000598587	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	escitalopram	0.040140272	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	citalopram	0.048015822	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	amitriptyline	0.019199168	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	imipramine	0.001382505	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	trimipramine	5.61573E-06	0.0330743

CYP2C19*2	CYP2C19*8	PM	lower dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	doxepin	0.00405065	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	sertraline	0.059227331	0.0330743
CYP2C19*2	CYP2C19*2	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*3	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*4	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*5	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*6	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*2	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*2	CYP2C19*2	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	desipramine	0.000369207	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*8	PM	lower dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*2	CYP2C19*2	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*3	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*4	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*5	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*6	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*7	PM	lower dose	nortriptyline	0.005517667	0.0330743

CYP2C19*2	CYP2C19*8	PM	lower dose	nortriptyline	0.005517667	0.0330743
CYP2C19*2	CYP2C19*2	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*3	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*4	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*5	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*6	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*2	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.0702023
CYP2C19*3	CYP2C19*3	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	trimipramine	5.61573E-06	0.0330743

CYP2C19*3	CYP2C19*4	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*3	CYP2C19*3	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*4	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*5	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*6	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*3	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*3	CYP2C19*3	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*3	CYP2C19*3	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*4	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*5	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*6	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*7	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*3	CYP2C19*3	PM	moniter serum level	voriconazole	0.000118223	0.0330743

CYP2C19*3	CYP2C19*4	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*3	CYP2C19*5	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*3	CYP2C19*6	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*3	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*3	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*3	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*4	CYP2C19*4	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743

CYP2C19*4	CYP2C19*4	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*4	CYP2C19*4	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*4	CYP2C19*5	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*4	CYP2C19*6	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*4	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*4	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*4	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*4	CYP2C19*4	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*4	CYP2C19*4	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*4	CYP2C19*5	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*4	CYP2C19*6	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*4	CYP2C19*7	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*4	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*4	CYP2C19*4	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*4	CYP2C19*5	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*4	CYP2C19*6	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*4	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*4	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*4	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*5	CYP2C19*5	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	citalopram	0.048015822	0.0330743

CYP2C19*5	CYP2C19*6	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*5	CYP2C19*5	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*5	CYP2C19*6	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*5	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*5	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*5	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*5	CYP2C19*5	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*5	CYP2C19*5	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*5	CYP2C19*6	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*5	CYP2C19*7	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*5	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*5	CYP2C19*5	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*5	CYP2C19*6	PM	moniter serum level	voriconazole	0.000118223	0.0330743

CYP2C19*5	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*5	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*5	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*6	CYP2C19*6	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*6	CYP2C19*6	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*6	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*6	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*6	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*6	CYP2C19*6	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*6	CYP2C19*6	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*6	CYP2C19*7	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*6	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*6	CYP2C19*6	PM	moniter serum level	voriconazole	0.000118223	0.0330743

CYP2C19*6	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*6	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*6	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*7	CYP2C19*7	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*7	CYP2C19*7	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*7	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*7	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366
CYP2C19*7	CYP2C19*7	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*7	CYP2C19*7	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*7	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*7	CYP2C19*7	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*7	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*7	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
CYP2C19*8	CYP2C19*8	PM	reduce dose	clomiprimine	0.000598587	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	escitalopram	0.040140272	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	citalopram	0.048015822	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	amitriptyline	0.019199168	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	imipramine	0.001382505	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	trimipramine	5.61573E-06	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	doxepin	0.00405065	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	sertraline	0.059227331	0.0330743
CYP2C19*8	CYP2C19*8	PM	do not use	clopidogrel	0.026818778	0.0330743
CYP2C19*8	CYP2C19*17	IM	do not use	clopidogrel	0.026818778	0.2755366

CYP2C19*8	CYP2C19*8	PM	reduce dose	desipramine	0.000369207	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	protriptyline	6.21277E-05	0.0330743
CYP2C19*8	CYP2C19*8	PM	reduce dose	nortriptyline	0.005517667	0.0330743
CYP2C19*8	CYP2C19*8	PM	moniter serum level	voriconazole	0.000118223	0.0330743
CYP2C19*8	CYP2C19*17	IM	monitor serum level	voriconazole	0.000118223	0.2755366
						0
CYP2C9*1	CYP2C9*2	IM	reduce dose	phenytoin	0.005406706	0.281289
CYP2C9*1	CYP2C9*3	IM	reduce dose	phenytoin	0.005406706	0.281289
CYP2C9*1	CYP2C9*2	IM	reduce dose	warfarin	0.051141392	0.281289
CYP2C9*1	CYP2C9*3	IM	reduce dose	warfarin	0.051141392	0.281289
CYP2C9*1	CYP2C9*2	IM	reduce dose	celecoxib	0.012455696	0.281289
CYP2C9*1	CYP2C9*3	IM	reduce dose	celecoxib	0.012455696	0.281289
CYP2C9*2	CYP2C9*2	PM	reduce dose	phenytoin	0.005406706	0.033258
CYP2C9*2	CYP2C9*3	PM	reduce dose	phenytoin	0.005406706	0.033258
CYP2C9*2	CYP2C9*2	PM	reduce dose	warfarin	0.051141392	0.033258
CYP2C9*2	CYP2C9*3	PM	reduce dose	warfarin	0.051141392	0.033258
CYP2C9*2	CYP2C9*2	PM	reduce dose	celecoxib	0.012455696	0.033258
CYP2C9*2	CYP2C9*3	PM	reduce dose	celecoxib	0.012455696	0.033258
CYP2C9*3	CYP2C9*3	PM	reduce dose	phenytoin	0.005406706	0.033258
CYP2C9*3	CYP2C9*3	PM	reduce dose	warfarin	0.051141392	0.033258
CYP2C9*3	CYP2C9*3	PM	reduce dose	celecoxib	0.012455696	0.033258
CYP3A5*1	CYP3A5*2	IM	change dose	tacrolimus	0.002515466	0.058718273
CYP3A5*1	CYP3A5*3	IM	change dose	tacrolimus	0.002515466	0.182786656
CYP3A5*1	CYP3A5*6	IM	change dose	tacrolimus	0.002515466	0.017958538
CYP3A5*1	CYP3A5*7	IM	change dose	tacrolimus	0.002515466	0.01925352
DPYD rs67376798A	DPYD rs67376798A	PM	use other drug	capecitabine	0.000270053	0.000316526
DPYD rs67376798A	DPYD rs67376798A	PM	use other drug	fluorouracil	0.002248282	0.000316526
DPYD*1	DPYD*2A	IM	50% dose reduction	capecitabine	0.000270053	0.013210141
DPYD*1	DPYD*13	IM	50% dose reduction	capecitabine	0.000270053	0.001532499
DPYD*1	DPYD rs67376798A	IM	50% dose reduction	capecitabine	0.000270053	0.032754607
DPYD*1	DPYD*2A	IM	50% dose reduction	fluorouracil	0.002248282	0.013210141
DPYD*1	DPYD*13	IM	50% dose reduction	fluorouracil	0.002248282	0.001532499
DPYD*1	DPYD rs67376798A	IM	50% dose reduction	fluorouracil	0.002248282	0.032754607
DPYD*13	DPYD*13	PM	use other drug	capecitabine	0.000270053	7.701E-07
DPYD*13	DPYD rs67376798A	PM	use other drug	capecitabine	0.000270053	0.000015402
DPYD*13	DPYD*13	PM	use other drug	fluorouracil	0.002248282	7.701E-07

DPYD*13	DPYD rs67376798A	PM	use other drug	fluorouracil	0.002248282	0.000015402
DPYD*2A	DPYD*2A	PM	use other drug	capecitabine	0.000270053	5.72218E-05
DPYD*2A	DPYD*13	PM	use other drug	capecitabine	0.000270053	1.32765E-05
DPYD*2A	DPYD rs67376798A	PM	use other drug	capecitabine	0.000270053	0.00026553
DPYD*2A	DPYD*2A	PM	use other drug	fluorouracil	0.002248282	5.72218E-05
DPYD*2A	DPYD*13	PM	use other drug	fluorouracil	0.002248282	1.32765E-05
DPYD*2A	DPYD rs67376798A	PM	use other drug	fluorouracil	0.002248282	0.00026553
G6PD I	G6PD I	severe deficiency	use other drug	rasburicase	1.86672E-08	0
G6PD I	G6PD I	severe deficiency	use other drug	methylene blue	1.83561E-07	0
G6PD II	G6PD II	10-60% of normal	use other drug	rasburicase	1.86672E-08	0.000003584
G6PD II	G6PD III	10-60% of normal	use other drug	rasburicase	1.86672E-08	0
G6PD II	G6PD II	10-60% of normal	use other drug	methylene blue	1.83561E-07	0.000003584
G6PD II	G6PD III	10-60% of normal	use other drug	methylene blue	1.83561E-07	0
G6PD III	G6PD III	10-60% of normal	use other drug	rasburicase	1.86672E-08	0.003698081
G6PD III	G6PD III	10-60% of normal	use other drug	methylene blue	1.83561E-07	0.003698081
HLA-B*15:02:01		use other drug		phenytoin	0.005406706	0.2150754
HLA-B*15:02:01		use other drug		carbamazepine	0.005733557	0.2150754
HLA-B*57:01:01		use other drug		abacavir	0.000137142	0.1091776
HLA-B*58:01:01		use other drug		allopurinol	0.019266523	0.0284902
IFNL-3: T	IFNL-3; C		unfavorable	ribavirin	0.000205209	0.39596586
IFNL-3: T	IFNL-3: T		unfavorable	ribavirin	0.000205209	0.13415075
IFNL-3: T	IFNL-3; C		unfavorable	bocepevir	9.42695E-07	0.39596586
IFNL-3: T	IFNL-3: T		unfavorable	bocepevir	9.42695E-07	0.13415075
IFNL-3: T	IFNL-3; C		unfavorable	telaprevir	7.80913E-07	0.39596586
IFNL-3: T	IFNL-3: T		unfavorable	telaprevir	7.80913E-07	0.13415075
SLCO1B1*1	SLCO1B1*5	IM	lower dose or alt	simvastatin	0.076296724	0.013153308
SLCO1B1*1	SLCO1B1*15	IM	lower dose or alt	simvastatin	0.076296724	0.1993924
SLCO1B1*1	SLCO1B1*17	IM	lower dose or alt	simvastatin	0.076296724	0.1993924
SLCO1B1*15	SLCO1B1*15	PM	lower dose or alt	simvastatin	0.076296724	0.016736013
SLCO1B1*15	SLCO1B1*17	PM	lower dose or alt	simvastatin	0.076296724	0.033472026
SLCO1B1*17	SLCO1B1*17	PM	lower dose or alt	simvastatin	0.076296724	0.016736013

SLCO1B1*5	SLCO1B1*5	PM	lower dose or alt	simvastatin	0.076296724	0.002358526
SLCO1B1*5	SLCO1B1*15	PM	lower dose or alt	simvastatin	0.076296724	0.003841151
SLCO1B1*5	SLCO1B1*17	PM	lower dose or alt	simvastatin	0.076296724	0.003841151
TPMT *3B	TPMT *3B	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	1.63662E-07
TPMT *3B	TPMT *3C	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	2.98569E-06
TPMT *3B	TPMT*4	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	4.26019E-06
TPMT *3B	TPMT *3B	PM	use other drug	azathioprine	0.002105378	1.63662E-07
TPMT *3B	TPMT *3C	PM	use other drug	azathioprine	0.002105378	2.98569E-06
TPMT *3B	TPMT*4	PM	use other drug	azathioprine	0.002105378	4.26019E-06
TPMT *3B	TPMT *3B	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	1.63662E-07
TPMT *3B	TPMT *3C	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	2.98569E-06
TPMT *3B	TPMT*4	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	4.26019E-06
TPMT *3C	TPMT *3C	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	0.000704647
TPMT *3C	TPMT*4	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	3.88592E-05
TPMT *3C	TPMT *3C	PM	use other drug	azathioprine	0.002105378	0.000704647
TPMT *3C	TPMT*4	PM	use other drug	azathioprine	0.002105378	3.88592E-05
TPMT *3C	TPMT *3C	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	0.000704647
TPMT *3C	TPMT*4	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	3.88592E-05
TPMT*1	TPMT*2	IM	lower dose	thioguanine	5.84284E-06	0.003134738
TPMT*1	TPMT*3A	IM	lower dose	thioguanine	5.84284E-06	0.055365231
TPMT*1	TPMT *3B	IM	lower dose	thioguanine	5.84284E-06	0.000710032
TPMT*1	TPMT *3C	IM	lower dose	thioguanine	5.84284E-06	0.021257322
TPMT*1	TPMT*4	IM	lower dose	thioguanine	5.84284E-06	0.0092412
TPMT*1	TPMT*2	IM	lower dose	azathioprine	0.002105378	0.003134738
TPMT*1	TPMT*3A	IM	lower dose	azathioprine	0.002105378	0.055365231
TPMT*1	TPMT *3B	IM	lower dose	azathioprine	0.002105378	0.000710032
TPMT*1	TPMT *3C	IM	lower dose	azathioprine	0.002105378	0.021257322
TPMT*1	TPMT*4	IM	lower dose	azathioprine	0.002105378	0.0092412
TPMT*1	TPMT*2	IM	lower dose	mercaptopurine	0.000588765	0.003134738

TPMT*1	TPMT*3A	IM	lower dose	mercaptopurine	0.000588765	0.055365231
TPMT*1	TPMT *3B	IM	lower dose	mercaptopurine	0.000588765	0.000710032
TPMT*1	TPMT *3C	IM	lower dose	mercaptopurine	0.000588765	0.021257322
TPMT*1	TPMT*4	IM	lower dose	mercaptopurine	0.000588765	0.0092412
TPMT*2	TPMT*2	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	2.94641E-06
TPMT*2	TPMT*3A	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	0.000104595
TPMT*2	TPMT *3B	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	1.34906E-06
TPMT*2	TPMT *3C	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	2.27023E-05
TPMT*2	TPMT*4	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	1.75583E-05
TPMT*2	TPMT*2	PM	use other drug	azathioprine	0.002105378	2.86324E-06
TPMT*2	TPMT*3A	PM	use other drug	azathioprine	0.002105378	0.000104595
TPMT*2	TPMT *3B	PM	use other drug	azathioprine	0.002105378	1.34906E-06
TPMT*2	TPMT *3C	PM	use other drug	azathioprine	0.002105378	2.27023E-05
TPMT*2	TPMT*4	PM	use other drug	azathioprine	0.002105378	1.75583E-05
TPMT*2	TPMT*2	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	2.86324E-06
TPMT*2	TPMT*3A	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	0.000104595
TPMT*2	TPMT *3B	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	1.34906E-06
TPMT*2	TPMT *3C	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	2.27023E-05
TPMT*2	TPMT*4	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	1.75583E-05
TPMT*3A	TPMT*3A	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	0.000976515
TPMT*3A	TPMT *3B	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	2.52771E-05
TPMT*3A	TPMT *3C	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	0.000256765
TPMT*3A	TPMT*4	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	0.000328987
TPMT*3A	TPMT*3A	PM	use other drug	azathioprine	0.002105378	0.000976515
TPMT*3A	TPMT *3B	PM	use other drug	azathioprine	0.002105378	2.52771E-05
TPMT*3A	TPMT *3C	PM	use other drug	azathioprine	0.002105378	0.000256765

TPMT*3A	TPMT*4	PM	use other drug	azathioprine	0.002105378	0.000328987
TPMT*3A	TPMT*3A	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	0.000976515
TPMT*3A	TPMT *3B	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	2.52771E-05
TPMT*3A	TPMT *3C	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	0.000256765
TPMT*3A	TPMT*4	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	0.000328987
TPMT*4	TPMT*4	PM	use alt drug or 90% dose reduce	thioguanine	5.84284E-06	2.77236E-05
TPMT*4	TPMT*4	PM	use other drug	azathioprine	0.002105378	2.77236E-05
TPMT*4	TPMT*4	PM	use alt drug or 90% dose reduce	mercaptopurine	0.000588765	2.77236E-05
UGT1A1 *28	UGT1A1 *28	PM	dose change	irinotecan	2.25251E-06	0.09839775
UGT1A1*1	UGT1A1 *28	IM	dose change	irinotecan	2.25251E-06	0.404637014
UGT1A1*6	UGT1A1*6	PM	dose change	irinotecan	2.25251E-06	0.001251469
UGT1A1*6	UGT1A1 *28	PM	dose change	irinotecan	2.25251E-06	0.007143267
VKORC1	CT		change dose	warfarin	0.051141392	0.422125311
VKORC1	TT		change dose	warfarin	0.051141392	0.188495045
VKORC1	CC		change dose	warfarin	0.051141392	0.348079645
VKORC1	GG		change dose	warfarin	0.051141392	0.348079645
VKORC1	GA		change dose	warfarin	0.051141392	0.422125311
VKORC1	AA		change dose	warfarin	0.051141392	0.188495045

APPENDIX E - SAS CODE FOR MONTE CARLO SENSITIVITY ANALYSIS OF ERROR

```
*****   Calculating Aggragate Number Needed to Screen, with Monte Carlo
Analysis Based 95% Confidence Interval for CUMC data  ****;

/* 'DRPH.Action_Table' holds the observed values for 4 variables: Allele1,
Allele2, Actionable and Drug.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Actionable-- is a binary variable determined by whether there is an
actionable guideline for this genotype drug combination*/
/* Drug-- is the name of the drug in the guideline.*/

/* 'DRPH.Allele_Frequencies' holds the observed values for three variables
Allele1, Allele2, and Population_frequency.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Population_Frequency-- is the reported allele frequency in an enthicity
adjusted general population*/

/* Sort BY is used to merge 'DRPH.Action_Table' and
'DRPH.CUMC_Genotype_Frequencies' in reference to 'Allele1' and 'Allele2' */

DATA Allele_Transition_Table1;

set DRPH.Allele_Frequencies;

Allele1=Gene;
Allele2=Gene;
population_frequency1=population_frequency;
population_frequency2=population_frequency;

RUN;

DATA Allele_Transition_Table2;

if 0 then set Allele_Transition_Table1 (keep= Allele1 population_frequency1);
      declare hash hmerge(dataset: 'Allele_Transition_Table1');
            rc1 = hmerge.defineKey('Allele1');
            rc2 = hmerge.defineData('population_frequency1');
            rc3 = hmerge.defineDone();
      do until(done);
            set DRPH.Action_Table (keep= Allele1 Allele2 Actionable Drug)
end=done;
            rc4 = hmerge.find();
            if rc4 = 0 then output Allele_Transition_Table2;
      end;
      stop;


DATA Allele_Transition_Table3;

if 0 then set Allele_Transition_Table1 (keep= Allele2 population_frequency2);
      declare hash hmerge(dataset: 'Allele_Transition_Table1');
            rc1 = hmerge.defineKey('Allele2');
            rc2 = hmerge.defineData('population_frequency2');
```

```
            rc3 = hmerge.defineDone();
      do until(done);
            set Allele_Transition_Table2 (keep= Allele1 Allele2
population_frequency1 Actionable Drug) end=done;
            rc4 = hmerge.find();
            if rc4 = 0 then output Allele_Transition_Table3;
      end;
      stop;


      /* convert drug names to all caps in 'Allele_Transition_Table' for hash
object key matching and create a variable name that will match the key.*/
/* for the hash object defined below. */

DATA Cap_Allele_Transition_Table;

Set Allele_Transition_Table3;

 Combined_Molecule=UPCASE(Drug);

RUN;
/* the hash object 'hmerge' is created to add the frequency of observed NRx
for each drug */
DATA Drug_Transition_Table;

if 0 then set DRPH.odrugrisktotal (keep= Combined_Molecule
NRx_MAT__Feb_2015);
      declare hash hmerge(dataset:'DRPH.odrugrisktotal');
            rc1 = hmerge.defineKey('Combined_Molecule');
            rc2 = hmerge.defineData('NRx_MAT__Feb_2015');
            rc3 = hmerge.defineDone();
      do until(done);
            set Cap_Allele_Transition_Table  end=done;
            rc4 = hmerge.find();
            if rc4 = 0 then output Drug_Transition_Table;
      end;
      stop;


/* both the absolute risk reduction weighted for genotype change and drug
exposure chance is calculated for each genotype drug pair.*/
/* a standard error is calculated for both the genotype chance and drug
exposure chance based on the large N approximation of the normal distribution
to the */
/* binomial distribution if the number of observations are known.  If they
are not known then the smallest noted number of observations from the
literature is used.*/
/* In order to estimate the 95% confidence interval generate a random point
measurement for the chance of drug exposure 'sDrugChance', the chance of
having a specific genotype 'sGenotypeChance' */
/* related to knowing the genotype.  A normal distribution is used because,
for large n it approaches the binomial distribution and can be calculated
from frequency data and N. */


DATA Obs_Transition_Table;
     SET Drug_Transition_Table;
```

```
             /* discard non-actionable entires in the table */
       IF actionable=1;

/* to obtain the number needed to screen and an approximation of the 95%
confidence interval the inverse of the */
/* aggregate absolute risk reduction both observed and simulated are
calculated.*/

            oDrugChance= NRx_MAT__Feb_2015/321418820.0; /* total 2015
population estimate from the US Census Bureau */

            /* the total number of observations is at least the number of new
perscriptions */
            DrugChanceSD= SQRT(oDrugChance*(1.0-oDrugChance));


            If (Allele1 EQ Allele2) Then oGenoChance=
population_frequency1**2;
            Else oGenoChance=2.0*population_frequency1*population_frequency2;

            oAllele1=population_frequency1;
            oAllele2=population_frequency2;

            oAllele1SD=SQRT(oAllele1*(1.0-oAllele1));
            oAllele2SD=SQRT(oAllele2*(1.0-oAllele2));
            oArr=oDrugChance*oGenoChance;

      Run;

DATA Sim_Transition_Table;
     SET Obs_Transition_Table;
       ARRAY sArr(1000) sArr1-sArr1000;

/*For a point estimate, calculate the observed aggregate number needed to
screen 'oANNS' based on the individual drug exposure chance means, */
/* genotype chance means based on observations. */

/* In order to estimate the 95% confidence interval generate a random point
measurement for the chance of drug exposure 'sDrugChance', the chance of
having a specific genotype 'sGenotypeChance' */
/* and the absolute risk reduction related to knowing the genotype. */
      DO I=1 to 1000;
            /* Check to make sure standard deviation values are non-zero. If
they are zero, use the mean value without variation since it would be very
small.*/
            IF (DrugChanceSD NE 0.0) Then sDrugChance=RAND('Normal',
oDrugChance, DrugChanceSD);
            Else sDrugChance=oDrugChance;

            IF (oAllele1SD NE 0.0) Then sAllele1=RAND('Normal',
population_frequency1, oAllele1SD);
            Else sAllele1=population_frequency1;

            IF(oAllele2SD NE 0.0) Then sAllele2=RAND('Normal',
population_frequency2, oAllele2SD);
```

```
            Else sAllele2=population_frequency2;

            If (Allele1 EQ Allele2) Then sGenoChance= sAllele1**2;
            Else sGenoChance=2.0*sAllele1*sAllele2;
            sArr(I)=sDrugChance*sGenoChance;

            END;
            RUN;


DATA SUM_Transition_Table;
set Sim_Transition_Table;
 ARRAY sArr(1000) sArr1-sArr1000;
 ARRAY SumArray (1000) SumArray1-SumArray1000;

      RETAIN oAArr SumArray1-SumArray1000 0.0;

        DO J=1 to 1000;
            SumArray(J)+sArr(J);
        END;

      oAArr+oArr;

      RUN;

      DATA sResultsANNS;
      ARRAY sArr(1000) sArr1-sArr1000;
      ARRAY SumArray(1000) SumArray1-SumArray1000;
      ARRAY sANNS(1000) sANNS1-sANNS1000;
      SET SUM_Transition_Table;

  DO J=1 to 1000;
      sANNS(J)=1.0/MAX(SumArray(J));
  END;

oANNS=1.0/MAX(oAArr);

      RUN;

DATA oANNS_Result;

Set sResultsANNS(keep=oANNS );

Observed_Aggrigate_NNS= MAX(oANNS);

     RUN;

Proc Print Data=oANNS_Result;
RUN;

DATA sCL_Result;

Set sResultsANNS(keep=sANNS1-sANNS1000);


     RUN;
```

```
/* Use the simulated aggregate number needed to screen values 'sANNS' to
calculate the 95% confidence interval for the observed aggregate number
needed to screen */
/* 'oANNS'.*/

/* the data set is transposed so that the 1000 simulated ANNS values can be
analysed as individual observations using Pro Means, */

       Proc Transpose DATA=sCL_Result OUT=sCL_Result_Transposed;
      RUN;

       PROC MEANS DATA=sCL_Result_Transposed N MEAN CLM RANGE;
       VAR COL996;

       RUN;
```

APPENDIX F - SAS PROGRAM FOR NCGENES DATA AND MONTE CARLO SIMULATION

```
*****   Calculating Aggregate Number Needed to Screen, with Monte Carlo
Analysis Based 95% Confidence Interval for CUMC data  ****;

/* 'DRPH.Action_Table' holds the observed values for 4 variables: Allele1,
Allele2, Actionable and Drug.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Actionable-- is a binary variable determined by whether there is an
actionable guideline for this genotype drug combination*/
/* Drug-- is the name of the drug in the guideline.*/

/* 'DRPH.CUMC_Genotype_Frequencies' holds the observed values for three
variables Allele1, Allele2, and frequency.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Frequency-- is the number of times the genotype was observed in the CUMC
dataset*/

/* the hash object 'hmerge' is created to add the frequency of observed NRx
for each drug */

DATA Obs_Transition_Table;
     SET DRPH.ncgene_data;


/* both the absolute risk reduction weighted for genotype change and drug
exposure chance is calculated for each genotype drug pair.*/
/* a standard error is calculated for both the genotype chance and drug
exposure chance based on the large N approximation of the normal distribution
to the */
/* binomial distribution if the number of observations are known.  If they
are not known then the smallest noted number of observations from the
literature is used.*/
/* In order to estimate the 95% confidence interval generate a random point
measurement for the chance of drug exposure 'sDrugChance', the chance of
having a specific genotype 'sGenotypeChance' */
/* related to knowing the genotype.  A normal distribution is used because,
for large n it approaches the binomial distribution and can be calculated
from frequency data and N. */


       /* total 2015 population estimate from the US Census Bureau */
            oDrugChance=chance_of_drug_exposure;

            oDrugChanceSD=SQRT(oDrugChance*(1.0-
oDrugChance)/number_of_drug_rx);

/* standard error of the mean for large N approximation of normal
distribution to binomial distribution. */

            oGenoChance= genotype_frequency;

            oGenoChanceSD= SQRT(oGenoChance*(1.0-
oGenoChance)/number_of_cases);
```

```
            oArr=oDrugChance*oGenoChance;

      Run;

      /* Monte Carlo simulation of 1000 data points for each drug phenotype
pair are created and the absolute reduction for each data point is
calculated. */

DATA Sim_Transition_Table;
     SET Obs_Transition_Table;
       ARRAY sArr(1000) sArr1-sArr1000;

      DO I=1 to 1000;

            IF (DrugChanceSD NE 0.0) Then sDrugChance=ABS(RAND('Normal',
oDrugChance, oDrugChanceSD));
            Else sDrugChance=oDrugChance;

            IF (oGenoChanceSD NE 0.0) Then sGenoChance=ABS(RAND('Normal',
oGenoChance, oGenoChanceSD));
            Else sGenoChance=oGenoChance;


            sArr(I)=sDrugChance*sGenoChance;

        END;


      RUN;

/* Both the observed absolute risk reduction from the absolute risk reduction
terms weighted for likelihood of drug exposure and */
/* the simulated absolute risk reduction terms weighted for likelihood of
genotype and drug exposure are aggregated to form the observed */
/* aggregate absolute risk reduction and 1000 simulated aggregate absolute
risk reduction point estimates respectively */

DATA SUM_Transition_Table;
 Set Sim_Transition_Table;
 ARRAY sArr(1000) sArr1-sArr1000;
 ARRAY SumArray(1000) SumArray1-SumArray1000;

      RETAIN oAArr SumArray1-SumArray1000 0.0;

        DO J=1 to 1000;
            SumArray(J)+sArr(J);
        END;

      oAArr+oArr;

      RUN;
/* to obtain the number needed to screen and an approximation of the 95%
confidence interval the inverse of the */
/* aggregate absolute risk reduction both observed and simulated are
calculated.*/

DATA sResultsANNS;
```

```
 ARRAY sArr(1000) sArr1-sArr1000;
 ARRAY SumArray(1000) SumArray1-SumArray1000;
 ARRAY sANNS(1000) sANNS1-sANNS1000;
 SET SUM_Transition_Table;

  DO J=1 to 1000;
      sANNS(J)=1.0/MAX(SumArray(J));
  END;

oANNS=1.0/MAX(oAArr);

      RUN;

DATA oANNS_Result;

Set sResultsANNS(keep=oANNS );

Observed_Aggrigate_NNS= MAX(oANNS);

     RUN;

Proc Print Data=oANNS_Result;
RUN;

DATA sCL_Result;

Set sResultsANNS(keep=sANNS1-sANNS1000);

     RUN;

/* Use the simulated aggregate number needed to screen values 'sANNS' to
calculate the 95% confidence interval for the observed aggregate number
needed to screen */
/* 'oANNS'.*/

/* the data set is transposed so that the 1000 simulated ANNS values can be
analyzed as individual observations using Pro Means, */

       Proc Transpose DATA=sCL_Result OUT=sCL_Result_Transposed;
      RUN;

       PROC MEANS DATA=sCL_Result_Transposed N MEAN CLM RANGE;
       VAR COL21;

       RUN;
```

APPENDIX G - SAS PROGRAM FOR CUMC DATA AND MONTE CARLO SIMULATION

```
*****   Calculating Aggregate Number Needed to Screen, with Monte Carlo
Analysis Based 95% Confidence Interval for CUMC data  ****;

/* 'DRPH.Action_Table' holds the observed values for 4 variables: Allele1,
Allele2, Actionable and Drug.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Actionable-- is a binary variable determined by whether there is an
actionable guideline for this genotype drug combination*/
/* Drug-- is the name of the drug in the guideline.*/

/* 'DRPH.CUMC_Genotype_Frequencies' holds the observed values for three
variables Allele1, Allele2, and frequency.*/
/* Allele1 and Allele2 --are the allele names ( ie *1) */
/* Frequency-- is the number of times the genotype was observed in the CUMC
dataset*/

DATA DRPH.CUMC_Genotypes_Concatonated;

SET DRPH.CUMC_Genotype_Frequency;
CONCATONATED_GENOTYPE=CAT(ALLELE1, ALLELE2);

RUN;

DATA DRPH.Action_Table_Concatonated;

SET DRPH.Action_Table;
CONCATONATED_GENOTYPE=CAT(ALLELE1, ALLELE2);

RUN;

DATA Allele_Transition_Table;

if 0 then set DRPH.CUMC_Genotypes_Concatonated (keep= CONCATONATED_GENOTYPE
COUNT);
      declare hash hmerge(dataset: 'DRPH.CUMC_Genotypes_Concatonated');
            rc1 = hmerge.defineKey('CONCATONATED_GENOTYPE');
            rc2 = hmerge.defineData('COUNT');
            rc3 = hmerge.defineDone();
      do until(done);
            set DRPH.Action_Table_Concatonated (keep= Allele1 Allele2
Actionable Drug CONCATONATED_GENOTYPE) end=done;
            rc4 = hmerge.find();
            if rc4 = 0 then output Allele_Transition_Table;
      end;
      stop;

/* convert drug names to all caps in 'Allele_Transition_Table' for hash
object key matching and create a variable name that will match the key.*/
/* for the hash object defined below. */

DATA Cap_Allele_Transition_Table;

Set Allele_Transition_Table;
```

```
 Combined_Molecule=UPCASE(Drug);

RUN;

/* the hash object 'hmerge' is created to add the frequency of observed NRx
for each drug */

DATA Drug_Transition_Table;

if 0 then set DRPH.odrugrisktotal (keep= Combined_Molecule
NRx_MAT__Feb_2015);
      declare hash hmerge(dataset:'DRPH.odrugrisktotal');
            rc1 = hmerge.defineKey('Combined_Molecule');
            rc2 = hmerge.defineData('NRx_MAT__Feb_2015');
            rc3 = hmerge.defineDone();
      do until(done);
            set Cap_Allele_Transition_Table  end=done;
            rc4 = hmerge.find();
            if rc4 = 0 then output Drug_Transition_Table;
      end;
      stop;

DATA Obs_Transition_Table;
     SET Drug_Transition_Table;

       /* discard non-actionable entries in the table */

       IF actionable=1;


/* both the absolute risk reduction weighted for genotype change and drug
exposure chance is calculated for each genotype drug pair.*/
/* a standard error is calculated for both the genotype chance and drug
exposure chance based on the large N approximation of the normal distribution
to the */
/* binomial distribution if the number of observations are known.  If they
are not known then the smallest noted number of observations from the
literature is used.*/
/* In order to estimate the 95% confidence interval generate a random point
measurement for the chance of drug exposure 'sDrugChance', the chance of
having a specific genotype 'sGenotypeChance' */
/* related to knowing the genotype.  A normal distribution is used because,
for large n it approaches the binomial distribution and can be calculated
from frequency data and N. */

       /* total 2015 population estimate from the US Census Bureau */
            oDrugChance= NRx_MAT__Feb_2015/321418820.0;

            oDrugChanceSD=SQRT(oDrugChance*(1.0-
oDrugChance)/NRx_MAT__Feb_2015);

/* standard error of the mean for large N approximation of normal
distribution to binomial distribution.*/

            Ngeno=2983.0;
```

```
            oGenoChance= Count/Ngeno;    /* genotype frequency divided by the
number of observations */

            oGenoChanceSD= SQRT(oGenoChance*(1.0-oGenoChance)/Ngeno);

            oArr=oDrugChance*oGenoChance;

      Run;

      /* Monte Carlo simulation of 1000 data points for each drug phenotype
pair are created and the absolute reduction for each data point is
calculated. */

DATA Sim_Transition_Table;
     SET Obs_Transition_Table;
       ARRAY sArr(1000) sArr1-sArr1000;

      DO I=1 to 1000;

            IF (oDrugChanceSD NE 0.0) THEN sDrugChance=ABS(RAND('Normal',
oDrugChance, oDrugChanceSD));
            ELSE sDrugChance= oDrugChance;

            IF (oGenoChanceSD NE 0.0) THEN sGenoChance=ABS(RAND('Normal',
oGenoChance, oGenoChanceSD));
            ELSE sGenoChance=oGenoChance;

            sArr(I)=sDrugChance*sGenoChance;
        END;

      RUN;

/* Both the observed absolute risk reduction from the absolute risk reduction
terms weighted for likelihood of drug exposure and */
/* the simulated absolute risk reduction terms weighted for likelihood of
genotype and drug exposure are aggregated to form the observed */
/* aggregate absolute risk reduction and 1000 simulated aggregate absolute
risk reduction point estimates respectively */

DATA SUM_Transition_Table;
 Set Sim_Transition_Table;
 ARRAY sArr(1000) sArr1-sArr1000;
 ARRAY SumArray(1000) SumArray1-SumArray1000;

      RETAIN oAArr SumArray1-SumArray1000 0.0;

        DO J=1 to 1000;
            SumArray(J)+sArr(J);
        END;

      oAArr+oArr;

      RUN;
/* to obtain the number needed to screen and an approximation of the 95%
confidence interval the inverse of the */
/* aggregate absolute risk reduction both observed and simulated are
calculated.*/
```

```
DATA sResultsANNS;
 ARRAY sArr(1000) sArr1-sArr1000;
 ARRAY SumArray(1000) SumArray1-SumArray1000;
 ARRAY sANNS(1000) sANNS1-sANNS1000;
 SET SUM_Transition_Table;

  DO J=1 to 1000;
      sANNS(J)=1.0/MAX(SumArray(J));
  END;

oANNS=1.0/MAX(oAArr);

      RUN;

DATA oANNS_Result;
Set sResultsANNS(keep=oANNS );
Observed_Aggrigate_NNS= MAX(oANNS);

    RUN;

Proc Print Data=oANNS_Result;
RUN;

DATA sCL_Result;

Set sResultsANNS(keep=sANNS1-sANNS1000);

     RUN;

/* Use the simulated aggregate number needed to screen values 'sANNS' to
calculate the 95% confidence interval for the observed aggragate number
needed to screen */
/* 'oANNS'.*/

/* the data set is transposed so that the 1000 simulated ANNS values can be
analysed as individual observations using Pro Means, */

       Proc Transpose DATA=sCL_Result OUT=sCL_Result_Transposed;
      RUN;

       PROC MEANS DATA=sCL_Result_Transposed N MEAN CLM RANGE;
       VAR COL23;

       RUN;
```

APPENDIX H – POST-STUDY SYSTEM USABILITY QUESTIONNAIRE (PSSUQ)[43]

Instructions and Items:
This questionnaire gives you an opportunity to tell us your reactions to the system you used. Your responses will help us understand what aspects of the system you are particularly concerned about and the aspects that satisfy you. To as great a degree as possible, think about all the tasks that you have done with the system while you answer these questions.
Please read each statement and indicate how strongly you agree or disagree with the statement by circling a number on the scale. (1 = strongly agree to 7 = strongly disagree)

1. Overall, I am satisfied with how easy it is to use this system.
2. It was simple to use this system.
3. I could effectively complete the tasks and scenarios using this system.
4. I was able to complete the tasks and scenarios quickly using this system.
5. I was able to efficiently complete the tasks and scenarios using this system.
6. I felt comfortable using this system.
7. It was easy to learn to use this system.
8. I believe I could become productive quickly using this system.
9. The system gave error messages that clearly told me how to fix problems.
10. Whenever I made a mistake using the system, I could recover easily and quickly.
11. The information (such as on-line help, on-screen messages and other documentation) provided with this system was clear.
12. It was easy to find the information I needed.
13. The information provided for the system was easy to understand.
14. The information was effective in helping me complete the tasks and scenarios.
15. The organization of information on the system screens was clear.
16. The interface of this system was pleasant.
17. I liked using the interface of this system.
18. This system has all the functions and capabilities I expect it to have.
19. Overall, I am satisfied with this system.

Rules for Calculating CSUQ/PSSUQ Scores

You can calculate four scores from the responses to the PSSUQ items:
* the overall satisfaction score (OVERALL), > Items 1 through 19
* system usefulness (SYSUSE), > Items 1 through 8
* information quality (INFOQUAL) > Items 9 through 15 and
* interface quality (INTERQUAL). > Items 16 through 18

APPENDIX I – NCGENES RESULTS BY PHENOTYPE, DRUG, ACTION, AND ARR

Allele 1	Allele 2	number of cases	drug	chance of drug exposure	Pheno-type	action	weighted ARR
CYP2C19 *1	CYP2C19* 4	3	clopidogrel	0.026818778	IM	do not use	0.000119727
CYP2C19 *1	CYP2C19* 4	3	voriconazole	0.000118223	IM	moniter serum level	5.2778E-07
HLA-B*57:01:0 1		37	abacavir	0.000137142		use another drug	7.55097E-06
TPMT*1	TPMT*2	1	azathioprine	0.002105378	IM	reduce dose	3.133E-06
TPMT*1	TPMT*2	1	mercaptopurin e	0.000588765	IM	reduce dose	8.76138E-07
TPMT*1	TPMT*2	1	thioguanine	5.84284E-06	IM	reduce dose	8.69471E-09
CYP2C9* 1	CYP2C9*2	114	celecoxib	0.012455696	IM	reduce dose	0.00211302
CYP2C9* 1	CYP2C9*3	56	celecoxib	0.012455696	IM	reduce dose	0.001037975
CYP2C9* 2	CYP2C9*2	3	celecoxib	0.012455696	PM	reduce dose	5.56058E-05
CYP2C9* 2	CYP2C9*3	5	celecoxib	0.012455696	PM	reduce dose	9.26763E-05
CYP2C9* 3	CYP2C9*3	1	celecoxib	0.012455696	PM	reduce dose	1.85353E-05
CYP2C9* 1	CYP2C9*2	114	phenytoin	0.005406706	IM	reduce dose	0.000917209
CYP2C9* 1	CYP2C9*3	56	phenytoin	0.005406706	IM	reduce dose	0.000450559
CYP2C9* 2	CYP2C9*2	3	phenytoin	0.005406706	PM	reduce dose	2.41371E-05
CYP2C9* 2	CYP2C9*3	5	phenytoin	0.005406706	PM	reduce dose	4.02285E-05
CYP2C9* 3	CYP2C9*3	1	phenytoin	0.005406706	PM	reduce dose	8.04569E-06
CYP2C9* 1	CYP2C9*2	114	warfarin	0.051141392	IM	reduce dose	0.008675772
CYP2C9* 1	CYP2C9*3	56	warfarin	0.051141392	IM	reduce dose	0.004261783
CYP2C9* 2	CYP2C9*2	3	warfarin	0.051141392	PM	reduce dose	0.00022831
CYP2C9* 2	CYP2C9*3	5	warfarin	0.051141392	PM	reduce dose	0.000380516
CYP2C9* 3	CYP2C9*3	1	warfarin	0.051141392	PM	reduce dose	7.61033E-05

APPENDIX J – CUMC RESULTS BY PHENOTYPE, DRUG, ACTION, AND ARR

Allele1	Allele2	Genotype frequency	Number of Cases	Drug	Chance of drug exposure	Pheno-type	Action	Weighted ARR
CYP2C19*2	CYP2C19*1	0.1240	370	clopidogrel	0.0268	IM	do not use	0.003324170
CYP2C19*2	CYP2C19*1	0.1240	370	voriconazole	0.0001	IM	monitor serum level	0.000012404
CYP2C19*2	CYP2C19*1	0.1240	370	phenytoin	0.0054	IM	reduce dose	0.000669796
CYP2C19*4	CYP2C19*2	0.0007	2	clopidogrel	0.0268	PM	do not use	0.000017968
CYP2C19*4	CYP2C19*2	0.0007	2	voriconazole	0.0001	PM	moniter serum level	0.000000067
CYP2C19*4	CYP2C19*2	0.0007	2	nortriptyline	0.0055	PM	lower dose	0.000003688
CYP2C19*4	CYP2C19*2	0.0007	2	protriptyline	0.0001	PM	lower dose	0.000000067
CYP2C19*4	CYP2C19*2	0.0007	2	desipramine	0.0004	PM	lower dose	0.000000268
CYP2C19*4	CYP2C19*2	0.0007	2	sertraline	0.0592	PM	lower dose	0.000039692
CYP2C19*4	CYP2C19*2	0.0007	2	doxepin	0.0041	PM	lower dose	0.000002749
CYP2C19*4	CYP2C19*2	0.0007	2	trimipramine	0.0000	PM	lower dose	0.000000003
CYP2C19*4	CYP2C19*2	0.0007	2	imipramine	0.0014	PM	lower dose	0.000000939
CYP2C19*4	CYP2C19*2	0.0007	2	amitriptyline	0.0192	PM	lower dose	0.000012873
CYP2C19*4	CYP2C19*2	0.0007	2	citalopram	0.0480	PM	lower dose	0.000032182
CYP2C19*4	CYP2C19*2	0.0007	2	escitalopram	0.0401	PM	lower dose	0.000026886
CYP2C19*4	CYP2C19*2	0.0007	2	clomiprimine	0.0006	PM	lower dose	0.000000402
CYP2C19*4	CYP2C19*1	0.0030	9	clopidogrel	0.0268	IM	do not use	0.000080858
CYP2C19*4	CYP2C19*1	0.0030	9	voriconazole	0.0001	IM	monitor serum level	0.000000302
CYP2C19*4	CYP2C19*1	0.0030	9	phenytoin	0.0054	IM	reduce dose	0.000016292
CYP2C19*8	CYP2C19*2	0.0007	2	clopidogrel	0.0268	PM	do not use	0.000017968
CYP2C19*8	CYP2C19*2	0.0007	2	voriconazole	0.0001	PM	moniter serum level	0.000000067
CYP2C19*8	CYP2C19*2	0.0007	2	nortriptyline	0.0055	PM	lower dose	0.000003688
CYP2C19*8	CYP2C19*2	0.0007	2	protriptyline	0.0001	PM	lower dose	0.000000067
CYP2C19*8	CYP2C19*2	0.0007	2	desipramine	0.0004	PM	lower dose	0.000000268
CYP2C19*8	CYP2C19*2	0.0007	2	sertraline	0.0592	PM	lower dose	0.000039692
CYP2C19*8	CYP2C19*2	0.0007	2	doxepin	0.0041	PM	lower dose	0.000002749
CYP2C19*8	CYP2C19*2	0.0007	2	trimipramine	0.0000	PM	lower dose	0.000000003
CYP2C19*8	CYP2C19*2	0.0007	2	imipramine	0.0014	PM	lower dose	0.000000939

CYP2C19*8	CYP2C19*2	0.0007	2	amitriptyline	0.0192	PM	lower dose	0.000012873
CYP2C19*8	CYP2C19*2	0.0007	2	citalopram	0.0480	PM	lower dose	0.000032182
CYP2C19*8	CYP2C19*2	0.0007	2	escitalopram	0.0401	PM	lower dose	0.000026886
CYP2C19*8	CYP2C19*2	0.0007	2	clomiprimine	0.0006	PM	lower dose	0.000000402
CYP2C19*8	CYP2C19*8	0.0003	1	clopidogrel	0.0268	PM	do not use	0.000008984
CYP2C19*8	CYP2C19*8	0.0003	1	voriconazole	0.0001	PM	moniter serum level	0.000000034
CYP2C19*8	CYP2C19*8	0.0003	1	nortriptyline	0.0055	PM	lower dose	0.000001844
CYP2C19*8	CYP2C19*8	0.0003	1	protriptyline	0.0001	PM	lower dose	0.000000034
CYP2C19*8	CYP2C19*8	0.0003	1	desipramine	0.0004	PM	lower dose	0.000000134
CYP2C19*8	CYP2C19*8	0.0003	1	sertraline	0.0592	PM	lower dose	0.000019846
CYP2C19*8	CYP2C19*8	0.0003	1	doxepin	0.0041	PM	lower dose	0.000001374
CYP2C19*8	CYP2C19*8	0.0003	1	trimipramine	0.0000	PM	lower dose	0.000000002
CYP2C19*8	CYP2C19*8	0.0003	1	imipramine	0.0014	PM	lower dose	0.000000469
CYP2C19*8	CYP2C19*8	0.0003	1	amitriptyline	0.0192	PM	lower dose	0.000006436
CYP2C19*8	CYP2C19*8	0.0003	1	citalopram	0.0480	PM	lower dose	0.000016091
CYP2C19*8	CYP2C19*8	0.0003	1	escitalopram	0.0401	PM	lower dose	0.000013443
CYP2C19*8	CYP2C19*8	0.0003	1	clomiprimine	0.0006	PM	lower dose	0.000000201
CYP2C19*8	CYP2C19*1	0.0027	8	clopidogrel	0.0268	IM	do not use	0.000071874
CYP2C19*8	CYP2C19*1	0.0027	8	voriconazole	0.0001	IM	monitor serum level	0.000000268
CYP2C19*8	CYP2C19*1	0.0027	8	phenytoin	0.0054	IM	reduce dose	0.000014482
CYP2C9*3	CYP2C9*3	0.0030	9	phenytoin	0.0054	PM	reduce dose	0.000016292
CYP2C9*3	CYP2C9*3	0.0030	9	celecoxib	0.0125	PM	reduce dose	0.000037714
CYP2C9*3	CYP2C9*1	0.0647	193	celecoxib	0.0125	IM	reduce dose	0.000808750
CYP2C9*3	CYP2C9*1	0.0647	193	phenytoin	0.0054	IM	reduce dose	0.000349380
CYP2C9*3	CYP2C9*1	0.0647	193	tacrolimus	0.0025	IM	change dose	0.000161750
DPYD rs67376798A	DPYD*1	0.0013	4	flourouracil	0.0022	IM	50% dose reduction	0.000002950
DPYD rs67376798A	DPYD*1	0.0013	4	capecitabine	0.0003	IM	50% dose reduction	0.000000402
DPYD*2A	DPYD*1	0.0034	10	flourouracil	0.0022	PM	use other drug	0.000007375
DPYD*2A	DPYD*1	0.0034	10	capecitabine	0.0003	PM	use other drug	0.000001006
SLCO1B1*5	SLCO1B1*1	0.1861	555	simvastatin	0.0763	IM	lower dose or alt	0.014195944
SLCO1B1*5	SLCO1B1*5	0.0191	57	simvastatin	0.0763	PM	lower dose or alt	0.001457962

TPMT*2	TPMT*1	0.0050	15	azathioprine	0.0000	IM	lower dose	0.000000030
TPMT*2	TPMT*1	0.0050	15	mercaptopurine	0.0021	IM	lower dose	0.000010560
TPMT*2	TPMT*1	0.0050	15	thioguanine	0.0001	IM	lower dose	0.000000302
TPMT*2	TPMT*2	0.0003	1	azathioprine	0.0000	PM	use other drug	0.000000002
TPMT*2	TPMT*2	0.0003	1	mercaptopurine	0.0021	PM	use other drug	0.000000704
TPMT*2	TPMT*2	0.0003	1	thioguanine	0.0001	PM	use other drug	0.000000020
TPMT*3A	TPMT*1	0.0178	53	thioguanine	0.0000	IM	lower dose	0.000000107
TPMT*3A	TPMT*1	0.0178	53	azathioprine	0.0021	IM	lower dose	0.000037311
TPMT*3A	TPMT*1	0.0178	53	mercaptopurine	0.0001	IM	lower dose	0.000001066
TPMT*3A	TPMT*3A	0.0007	2	thioguanine	0.0000	PM	use other drug	0.000000004
TPMT*3A	TPMT*3A	0.0007	2	azathioprine	0.0021	PM	use other drug	0.000001408
TPMT*3A	TPMT*3A	0.0007	2	mercaptopurine	0.0001	PM	use other drug	0.000000040
TPMT*3A	TPMT*3B	0.0251	75	thioguanine	0.0000	PM	use alt drug or 90% dose reduce	0.000000151
TPMT*3A	TPMT*3B	0.0251	75	azathioprine	0.0021	PM	use alt drug or 90% dose reduce	0.000052799
TPMT*3A	TPMT*3B	0.0251	75	mercaptopurine	0.0001	PM	use alt drug or 90% dose reduce	0.000001509
UGT1A1*6	UGT1A1*6	0.0007	2	irinotecan	0.0000	PM	dose change	0.000000002
G6PD II	G6PD II	0.0030	9	rasburicase	0.0000	10-60% of normal	use other drug	0.000000000
G6PD II	G6PD II	0.0030	9	methylene blue	0.0000	10-60% of normal	use other drug	0.000000001
G6PD II	G6PD III	0.0037	11	rasburicase	0.0000	10-60% of normal	use other drug	0.000000000
G6PD II	G6PD III	0.0037	11	methylene blue	0.0000	10-60% of normal	use other drug	0.000000001
G6PD III	G6PD III	0.0318	95	rasburicase	0.0000	10-60% of normal	use other drug	0.000000001
G6PD III	G6PD III	0.0318	95	methylene blue	0.0000	10-60% of normal	use other drug	0.000000006
total actionable genotypes			**1483**				**ARR=**	**0.021680452**
total observations			**2983**				**ANNS=**	**46.12449929**

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